DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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 Facsimile Transmission

JUN 23 2003

Patrick J. Daley, M.D.
1589 East 19th Street
Tulsa, Oklahoma 74120

Dear Dr. Daley:

The Food and Drug Administration (FDA) has investigated allegations that you failed to fulfill the responsibilities of a clinical investigator for a study utilizing an unlicensed biological investigational new drug, a [redacted] vaccine, in violation of FDA regulations governing investigational new drugs. Between July 19 and September 6, 2002, Janice Hickok and Marc Dickens, investigators from the FDA Dallas District Office, met with you, clinical study personnel, and your attorneys, to inspect the records relating to your use of the investigational [redacted] vaccine. This inspection was conducted as part of the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational products. The inspection focused on the study titled "*Safety and Efficacy of* [redacted] *Vaccine in* [redacted]"

The Form FDA 483 "List of Inspectional Observations" was presented and discussed with you and your representatives at the end of the inspection. Your attorney responded on your behalf in a letter to FDA dated September 20, 2002.

Based on the results of this inspection and on other information available to the Agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Parts 312 and 50. These regulations are available at http://www.access.gpo.gov/nara/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 drugs as set forth under 21 CFR § 312.70.

This letter includes allegations that did not appear on the Form FDA 483. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. You submitted false information to the sponsor in reports required by 21 CFR §§ 312.62 and 312.64. [21 CFR § 312.70].

A. You submitted false information to the sponsor purporting to document the administration of doses of study vaccine/placebo that were not, in fact, administered to the infant study subjects. Examples are shown in the following table. The table lists the false information you submitted to the sponsor: subject, date of dose administration, and identification number of the vial of study vaccine/placebo administered.

Subject	Dose	Date of Dose	Vial ID Number
[redacted]	2	09/11/01	57590
	3	11/21/01	66523
	2	10/04/01	60189
	3	10/24/01	63954
	2	10/04/01	59720
	3	12/01/01	68015
	2	10/24/01	63950
	3	12/01/01	68016
	2	10/24/01	62462
	3	01/08/02	73744

B. You submitted false information to the sponsor documenting the completion of post vaccination follow-up safety contacts that you failed to perform for the subjects listed in item 1A, above. You falsely reported that you contacted the subjects' parent or guardian to perform follow-up safety contacts on days 7, 14, and 42 after the administration of each dose of study vaccine/placebo even though you never administered these vaccine/placebo doses to the study subjects. You submitted this information to the sponsor by facsimile transmission after the purported day 7 follow-up contact and in the case report forms (CRFs) for follow-up on days 7, 14, and 42. The following table lists the dates that you reported that you completed follow-up safety contacts for vaccine/placebos that were not administered; this is not a complete list.

Subject	Date of Dose	Day 7 Facsimile	Day 7 CRF	Day 14 CRF	Day 42 CRF
[redacted]	9/11/01	9/17/01	9/17/01	9/24/01	10/22/01
	11/21/01	11/27/01	11/27/01	12/04/01	01/01/02
	10/04/01	10/10/01	10/10/01	10/17/01	11/14/01
	10/24/01	10/30/01	10/30/01	11/06/01	12/04/01
	10/04/01	10/10/01	10/10/01	10/17/01	11/14/01
	12/01/01	12/07/01	12/07/01	12/14/01	01/11/02
	10/24/01	10/30/01	10/30/01	11/06/01	*
	12/01/01	12/07/01	12/07/01	12/14/01	01/11/02
	10/24/01	10/30/01	10/30/01	11/06/01	12/04/01
	01/08/02	01/14/02	01/14/02	01/21/02	02/18/02

* The CRF states "3rd dose of vaccine given before 42nd day" however, neither dose 2 nor dose 3 were administered to subject [redacted]

In a "Memo to the File" dated May 31, 2002, you admitted "The majority of the day 7, 14, and 42 follow-up phone calls were not made nor were the 8 week mailers completed. It is not possible at this time to identify which patients were affected by this error."

C. You submitted false information to the sponsor regarding concomitant vaccines that were not administered to study subjects. The false information includes the dates of administration of the following vaccines: hepatitis B (Hep B); polio (IPV); diphtheria, tetanus, and pertussis (DTaP); *Haemophilus influenzae* type b (Hib); and Prevnar®. The case report forms falsely report that vaccines were administered even though these vaccinations are not documented in the subjects' medical records. In some cases, the subjects did not even visit your office on the dates you recorded on the case report forms. Furthermore, your medical records do not contain documentation of the dates that several subjects obtained concomitant vaccines through local health department clinics, yet you submitted those vaccination dates to the sponsor. Some of these purported Prevnar® injections would have occurred in April 2002 when there was, in fact, a shortage of the vaccine. The following table is not a complete list.

Subject	Date	Vaccine(s)		Subject	Date	Vaccine(s)
[redacted]	09/11/01	Hepatitis B, Prevnar®		[redacted]	01/08/02	Hepatitis B, Prevnar®
	11/21/01	DTaP, IPV, Hib			12/14/01	Hepatitis B, Prevnar®
	10/24/01	Hepatitis B, Prevnar®			10/11/01	Prevnar®
	09/09/01	DTaP, IPV, Hib			12/18/01	Prevnar®
	10/03/01	Hepatitis B, Prevnar®			10/25/01	Prevnar®
	08/06/01	DTaP, IPV, Hib			02/21/02	Hepatitis B, Prevnar®
	10/24/01	Hepatitis B, Prevnar®			02/01/02	DTaP, IPV, Hib
	11/29/01	Hepatitis B, Prevnar®			04/17/02	Hepatitis B
	10/24/01	Hepatitis B, Prevnar®			02/21/01	DTaP, IPV, Hib
	09/21/01	DTaP, IPV, Hib			03/19/02	Hepatitis B, Prevnar®
	11/01/01	Prevnar®			04/08/02	Hepatitis B, Prevnar®
	10/24/01	DTaP, IPV, Hib			03/07/02	DTaP, IPV, Hib
	10/24/01	DTaP, IPV, Hib			04/10/02	DTaP, IPV, Hib
	01/08/02	Hepatitis B, Prevnar®			03/27/02	DTaP, IPV, Hib
	12/02/01	Hepatitis B, Prevnar®			05/06/02	Hepatitis B, Prevnar®
	11/21/01	DTaP, IPV, Hib			04/24/02	Prevnar®

D. You submitted false information to the sponsor regarding the absence of serious adverse experiences. For example, you submitted the "Vaccination Visit 1 Follow-up Serious Adverse Experience" CRF to the sponsor documenting that subject [redacted] did not experience any serious adverse events during the protocol specified clinical follow-up period. Subject [redacted] was hospitalized and discharged from the hospital on day 42 of follow up after the administration of the first dose of study vaccine/placebo.

E. You affirmatively entered "rectal" as the method of temperature collection in the "Vaccination Visit" pages of the CRF submitted to the sponsor for each of the 264 subjects enrolled in the study. During the inspection, you stated that you in fact obtained each subject's temperature under the arm and then converted the temperature to an approximate rectal temperature. Protocol section I.D.2.e excludes subjects with fever at the time of immunization and defines fever as a **rectal** temperature greater than or equal to 38.1° C (100.5° F).

F. You entered false information in the "Contact Survey Information (6 week safety surveillance)" CRF. These CRFs are completed after each subject receives the final dose (dose 3 of 3 doses) of vaccine/placebo. You completed these CRFs for the subjects listed in the table below falsely reporting that you conducted safety monitoring with these subjects despite the fact that they did not even receive the final dose of vaccine/placebo.

Subject	Date	Week of Surveillance		Subject	Date	Week of Surveillance
[redacted]	1/02/02	6		[redacted]	2/23/02	12
	2/13/02	12			4/6/02	18
	3/27/02	18			2/19/02	6
	1/10/02	6			4/02/02	12
	2/21/02	12			1/13/02	6
	4/4/02	18			2/24/02	12
	12/5/01	6			4/7/02	18
	1/16/02	12			2/19/02	6
	2/27/02	18			4/02/02	12
	4/10/02	24			5/14/02	18
	1/12/02	6			4/06/02	6
	2/23/02	12			5/16/02	12
	4/6/02	18			4/18/02	6
	1/12/02	6			4/30/02	6
	2/23/02	12			4/30/02	6
	4/6/02	18			5/20/02	6
	1/12/02	6			6/11/02	12

2. You failed to maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation. [21 CFR § 312.62(b)].

A. You failed to document the occurrence and follow-up of Serious Adverse Experiences (SAEs) in the "Vaccination Visit 1 Follow-up Serious Adverse Experience" CRF and the "Vaccination Visit 1 Follow-up Contact Survey Information (Vaccination follow-up)" CRF and you falsely reported that there were no SAEs for these infant subjects. The protocol defines an

SAE as an event that, among other things, "results in or prolongs an existing inpatient hospitalization." Protocol section I.G requires follow-up for adverse experiences at days 7, 14, and 42 after each vaccine/placebo dose.

i. Subject [redacted] visited your office on [redacted] after experiencing "3 runny stools, one green." The subject was subsequently hospitalized and discharged from the hospital on [redacted]. The subject received the first dose of [redacted] vaccine/placebo on 11/19/01. The "Vaccination Visit 1 Follow-up Serious Adverse Experience" CRF for vaccination visit 1 follow-up dated 2/1/02 was marked "None" in response to the question: "Did any serious AEs occur during the protocol specified clinical follow-up period?"

Additionally, the "Vaccination Visit 1 Follow-up Contact Survey Information (Vaccination follow-up)" CRF for vaccination follow-up is marked "No" for day 42 of follow-up on 12/31/02 in response to the following two questions: "Were any serious adverse experiences reported by the parent/guardian?" and "Did the subject visit a health care facility for a stomach illness such as diarrhea and vomiting?" You signed this form on 2/1/02, [redacted] after the subject was discharged from the hospital.

ii. Subject [redacted] was hospitalized with abdominal pain from [redacted] to [redacted] and had a [redacted]. The subject received the first dose of [redacted] vaccine/placebo on 1/4/02. The "Vaccination Visit 1 Follow-up Serious Adverse Experience" CRF for vaccination visit 1 follow-up dated 2/4/02 was marked as "None" in response to the question: "Did any serious AEs occur during the protocol specified clinical follow-up period?" Additionally, the "Vaccination Visit 1 Follow-up Contact Survey Information (Vaccination follow-up)" CRF for vaccination follow-up states that contact was made on 01/17/02, [redacted] after hospital discharge. The response "No" is marked for the two following questions: "Were any serious adverse experiences reported by the parent/guardian?" and "Did the subject visit a health care facility for a stomach illness such as diarrhea and vomiting?"

iii. Subject [redacted] received the first dose of [redacted] vaccine/placebo on 1/4/02. According to the report submitted by the sponsor to the FDA on 1/8/02, the subject's parent contacted you on 1/5/02 to report diarrhea and blood in the stools. The subject was hospitalized from [redacted]. The "Vaccination Visit 1 Follow-up Serious Adverse Experience" CRF dated 3/19/02 is marked "None" for the occurrence of SAEs. The "Vaccination

Visit 1 Follow-up Contact Survey Information (Vaccination follow-up)" CRF entry dated 1/10/02 shows the response "No" is marked for the two following questions: "Were any serious adverse experiences reported by the parent/guardian?" and "Did the subject visit a health care facility for a stomach illness such as diarrhea and vomiting?"

B. You documented in the CRFs the administration of study vaccine/placebo to subjects who, in fact, did not receive the study drug. In addition to the subjects listed in item 1.A. above, the subjects listed in the following table did not receive doses of study vaccine/placebo as you recorded in their CRFs.

Subject	Dose	Date of Dose
[redacted]	3	12/01/01
	3	12/02/01
	3	01/08/02
	3	02/21/02
	2	02/01/02
	3	04/17/02
	3	03/07/02
	2	02/21/02
	3	05/07/02
	3	03/19/02
	3	03/19/02
	3	04/08/02
	3	04/17/02
	2	03/07/02
	2	03/07/02
	3	05/16/02
	3	04/17/02
	3	05/07/02
	3	05/08/02
	2	04/10/02
	2	04/25/02
	2	04/25/02
	2	05/13/02

C. For the subjects listed in item 1A and 2A above, you affixed into the "Vaccine Inventory and Label Log" CRF the tear-off labels removed from 33 vials of vaccine/placebo that you failed to administer to these subjects and documented the purported date of vaccine/placebo administration, the amount of vaccine/placebo administered, and the name of the person administering the vaccine/placebo for each vial. Further, you entered the name [redacted] your study coordinator, as the administrator of the 33 vaccine/placebo doses that were not given to the subjects.

D. You falsely documented in the "Vaccination Visit [2 or 3] Follow-up Contact Survey Information (Vaccination follow-up)" CRF the dates that you made follow up safety contacts with the subjects' parent/guardian on days 7, 14, and 42 after each purported vaccine/placebo dose for subjects who, in fact, did not even receive the study drug. Item 1.B. and the following table list the study subjects.

Subject	Dose	Date of Dose	Day 7	Day 14	Day 42
[redacted]	3	12/01/01	12/7/01	12/14/01	1/11/02
	3	12/02/01	12/7/01	12/14/01	1/12/02
	3	01/08/02	1/14/02	1/21/02	2/18/02
	3	02/21/02	2/27/02	3/6/02	4/3/02
	2	02/01/02	2/7/02	2/14/02	3/14/02
	3	04/17/02	4/23/02	4/30/02	*
	3	03/07/02	3/13/02	3/20/02	*
	2	02/21/02	2/27/02	3/6/02	4/4/02
	3	05/07/02	5/13/02	5/20/02	*
	3	03/19/02	3/25/02	4/1/02	4/29/02
	3	03/19/02	3/25/02	4/1/02	4/29/02
	3	04/08/02	4/14/02	4/21/02	5/19/02
	3	04/17/02	4/23/02	4/30/02	5/28/02
	2	03/07/02	3/13/02	3/20/02	4/18/02
	2	03/07/02	3/13/02	3/20/02	4/18/02
	3	05/16/02	5/22/02	*	*
	3	04/17/02	4/23/02	4/30/02	5/28/02
	3	05/07/02	5/13/02	5/20/02	*
	3	05/08/02	5/13/02	5/21/02	*
	2	04/10/02	4/16/02	4/23/02	5/21/02
	2	04/25/02	5/1/02	5/8/02	*
	2	04/25/02	5/1/02	5/8/02	*
	2	05/13/02	5/19/02	5/26/02	*

* No data entered on CRF at time of inspection

E. You failed to accurately document the administration of concomitant vaccines on the "Concomitant Non-Study Vaccine" CRF.

i. In some cases, the CRFs falsely report that concomitant vaccines were administered even though these vaccinations are not documented in the subjects' medical records. Examples include but are not limited to the following:

Subject	Date	Vaccine(s)
[redacted]	06/21/01	Hepatitis B, Prevnar®
	08/23/01	Hepatitis B, Prevnar®
	09/24/01	DTaP, IPV, Hib
	07/06/01	Hepatitis B
	09/11/01	DTaP, IPV, Hib, Prevnar®
	10/09/01	DTaP, IPV, Hib
	08/17/01	Prevnar®
	09/14/02	DTaP, IPV, Hib
	10/26/02	Hepatitis B, Prevnar®
	09/17/01	DTaP, IPV, Hib
	10/17/01	Hepatitis B, Prevnar®
	09/24/01	DTaP, IPV, Hib
	10/24/01	Hepatitis B, Prevnar®
	08/22/01	Prevnar®
	09/21/01	Hepatitis B, Prevnar®
	11/05/01	DTaP, IPV, Hib

Subject	Date	Vaccines
[redacted]	08/24/01	Hepatitis B, Prevnar®
	09/24/01	DTaP, IPV, Hib
	10/24/01	Hepatitis B, Prevnar®
	10/29/01	Hepatitis B
	11/30/01	DTaP, IPV, Hib
	01/07/02	Hepatitis B, Prevnar®
	12/11/01	DTaP, IPV, Hib
	01/30/02	Hepatitis B, Prevnar®
	01/04/02	Hepatitis B, Prevnar®
	02/08/02	DTaP, IPV, Hib
	03/08/02	Hepatitis B, Prevnar®
	02/28/02	DTaP, IPV, Hib
	04/02/02	Hepatitis B, Prevnar®
	01/21/02	Hepatitis B, Prevnar®
	02/22/02	DTaP, IPV, Hib
	04/05/02	Hepatitis B, Prevnar®

Additional examples include subjects: [redacted]

ii. In other cases, the CRFs are incomplete because they fail to document vaccines that were administered. Examples include the following:

Subject	Date	Vaccine(s)
[redacted]	07/06/01	Hepatitis B
	09/11/01	DTaP,IPV,Hib
	10/09/01	Hepatitis B
	08/17/01	DTaP,IPV,Hib
	09/14/01	Hepatitis B, Prevnar®
	10/26/02	DTaP,IPV,Hib
	08/24/01	DTaP,IPV,Hib
	09/24/01	Hepatitis B, Prevnar®
	10/29/01	DTaP,IPV,Hib
	11/30/01	Hepatitis B
	01/07/02	DTaP,IPV,Hib
	11/27/01	Hepatitis B, Prevnar®
	02/28/02	Hepatitis B, Prevnar®

Subject	Date	Vaccine(s)
[redacted]	04/02/02	DTaP,IPV,Hib
	01/21/02	DTaP,IPV,Hib
	02/22/02	Hepatitis B, Prevnar®
	04/05/02	DTaP,IPV,Hib
	03/18/02	Hepatitis B, Prevnar®
	03/27/02	Prevnar®
	05/28/02	Hepatitis B, Prevnar®
	06/04/02	Hepatitis B, Prevnar®
	06/06/02	Hepatitis B, Prevnar®
	06/27/02	Hepatitis B, Prevnar®
	05/08/02	Hepatitis B, Prevnar®
	05/30/02	Hepatitis B, Prevnar®

Additional examples include subjects: [redacted]

F. You failed to maintain clinical records as required by protocol section II.D. "Study Documentation and Records Retention." The patient history record was not present in the clinical chart for subject [redacted] at the time of inspection.

Your response letter acknowledges that you do not have the clinical records for subject [redacted]

G. You failed to prepare and maintain complete and accurate "Subject Vaccine Administration Records" (SVARs) for each subject receiving the study vaccine/placebo as required by the sponsor as part of the investigational plan.

i. You failed to prepare and maintain SVARs for subjects [redacted] through [redacted] and [redacted] through [redacted]

ii. The "Time Removed from the Refrigerator" and the "Time Administered" columns of the SVARs for subjects [redacted] through [redacted] are crossed out. The cross outs were not corrected, initialed, or dated.

iii. The number of vaccine/placebo doses administered listed on the SVARs do not agree with the number vaccine/placebo doses listed in the CRFs. For example, the "Vaccine Inventory and Label" CRF shows that subjects [redacted] received 3 doses of vaccine/placebo, and the SVARs show that subject [redacted] received two vaccine/placebo doses and that subjects [redacted] received a single vaccine/placebo dose.

H. You failed to maintain a complete and accurate "Subject Participation Log" as required by the sponsor as part of the investigational plan. The procedure for the "Subject Participation Log" states that "CURRENT STATUS OF THE SUBJECT ENROLLMENT MUST BE MAINTAINED AT ALL TIMES."

i. The "Subject Participation Log" at your site does not include entries for subjects [redacted] and [redacted]. In your response letter dated September 20, 2002, your attorney states that "Maintaining the Study Participation Log was not critical to the conduct of the study at this site" since you were "the only clinical investigator participating and he knew his patients well." On the contrary, as the regulations make clear, records of a clinical trial must be complete and accurate. Your attempt to suggest that an investigator who knows his patients may ignore the laws and

regulations governing clinical trials is wholly unacceptable. Indeed, the fact that you "were the only" clinical investigator makes it even more critical that you properly conduct the trial and properly record clinical information.

ii. You entered false information in the "Subject Participation Log." You falsely recorded the dates of vaccination visits for 18 subjects who failed to appear for 21 vaccination visits.

3. You failed to ensure that the investigation is conducted according to the investigational plan. [21 CFR § 312.60].

A. You failed to report Serious Adverse Experiences (SAEs) to the sponsor within 24 hours as required by protocol section I.G. Subjects [redacted] and [redacted] were hospitalized, yet your study records fail to document that you reported these SAEs to the sponsor within 24 hours as required by the protocol.

B. You failed to obtain each subject's temperature by the rectal method required by the protocol section I.D.2.e. During the inspection, you stated that you obtained each subject's temperature under the arm and converted the temperature to an approximate rectal temperature. See item 1E above.

C. Protocol section I.E.3 requires the collection of [redacted] from all subjects hospitalized [redacted] You failed to collect [redacted] specimens from subjects [redacted] who were hospitalized with symptoms of [redacted]

D. You administered the first dose of study vaccine/placebo to Subject [redacted] on 6/12/01 before you obtained the sponsor's waiver permitting you to enroll this ineligible subject on 6/13/01. Subject [redacted] had [redacted] disease [redacted] and had been treated with [redacted]. Protocol section I.D.2.g excludes from the trial subjects with "clinical evidence of active [redacted] illness or past diagnosis of severe [redacted] illness requiring surgery or that is currently controlled through medications such as [redacted] or [redacted] Furthermore, you falsely recorded "No" for the presence of this condition on the subject's case report form.

In your response letter dated September 20, 2002, your attorney states that the protocol "says infants with [redacted] that is well controlled with or without medications may participate in the study." This statement refers to an amendment to the protocol that went into effect in January 2002 that allows infants with well-controlled [redacted] to participate in the study. However, this amendment was not in effect at the time subject [redacted] was enrolled in the study.

E. You failed to complete "[redacted] Worksheets" for the infant subjects potentially experiencing [redacted] as required by the "Standard Operating Procedure for the Work-up of Cases of [redacted] for this study. Subject [redacted] had a [redacted] to rule out [redacted] Subjects [redacted] and [redacted] were hospitalized with symptoms of [redacted]

4. You failed to assure that the Institutional Review Board would be responsible for the continuing review and approval of the study by failing to submit complete and accurate information regarding the safety of the study. [21 CFR § 312.66].

A. You failed to report SAEs to the Institutional Review Board (IRB) within five days as required by the IRB. The IRB requires notification of "Serious adverse events including...hospitalizations or prolonging of hospitalization."

i. You failed to report to the IRB that subjects [redacted] and [redacted] were hospitalized.

ii. You failed to report to the IRB that subject [redacted] experienced [redacted] on 1/5/02 after receiving the first dose of vaccine/placebo on 1/4/02. On 1/8/02, subject [redacted] was hospitalized because the [redacted] was not resolved. A letter from the sponsor dated 1/24/02 reminded you to "Please notify the ERC [IRB] of this SAE."

iii. You failed to notify the IRB of the SAEs experienced by subjects [redacted] at the time you applied for continuing review of the study. You submitted the "Study Status Report/Reapproval Form" to the IRB on 4/2/02. In response to the question "Serious Adverse Event(s), Unexpected or Unusual Occurrence(s) in Subject(s) entered into study at your site?" [emphasis in original] you responded "NO." On 4/17/02 you resubmitted a corrected version of this form to the IRB, however, your response to this question remained "NO."

B. You failed to submit to the IRB any of the 18 eligibility waivers granted by the sponsor. The sponsor instructed you to provide a copy of these documents to the IRB. The sponsor approved waivers for 18 subjects who failed to meet eligibility requirements and/or the time interval between dose administrations required by the protocol.

C. In its decision to approve the consent forms for this study, the IRB expressly required that a third party witness the informed consent discussion, and that the witness document his/her presence with a signature. The IRB-approved consent form contained a space for the "Signature of Witness Other Than Person Obtaining Informed Consent." The majority of the informed consent forms were signed with the name [redacted] your study coordinator, written in a style that is not consistent with [redacted] signature on the "Site Signature Log." At the time of inspection, [redacted] was shown the signature and stated that it was not her signature and that she did not authorize anyone to sign her name on the consent forms.

During a site visit conducted June 19-21, 2001, you told a representative from [redacted] that you signed the name [redacted] on the informed consent form for subject [redacted], and you demonstrated the handwriting style you used to sign [redacted] name. The handwriting style used to sign [redacted] as the witness on the informed consent for subject [redacted] is virtually identical to the handwriting style of the name [redacted] on the informed consent forms of 195 additional study subjects.

In your response letter, your attorney argues on your behalf that "any irregularities related to signatures on study documents are potentially of significant concern to the agency. Nonetheless, the 483 includes observations in this regard that appears to be immaterial when viewed in context." Your response further states that even though the consent form had a witness signature line "the witness signature line could have been left blank on the informed consent forms" because a "short form" was not used to document informed consent, citing 21 CFR § 50.27(b)(2). We disagree. The IRB's requirement for the signature of a witness is provided in 21 CFR § 56.109(f): "An IRB...shall have the authority to observe or have a third party observe the consent process and the research." By falsely signing the witness' signature on these documents you deliberately misrepresented how you obtained the informed consent of the study subjects. We do not view this falsification as immaterial.

5. **You failed to obtain informed consent in accordance with the provisions of 21 CFR Parts 50 and 56. [21 CFR § 312.60].**

The informed consent form, collection of specimens for future analysis form, and/or the medical release forms for the infant subjects are missing critical information that is to be provided to ensure that you obtained adequate and legitimate informed consent.

A. The "VACCINE CONSENT FORM" and the "CONSENT FORM FOR THE COLLECTION OF SPECIMENS FOR FUTURE ANALYSIS" signed by the parent/legal guardian on 6/26/02 for subjects [redacted] and [redacted] do not contain the dated signature of the person obtaining the informed consent and the infant's name.

B. The parent/legal guardian's signature on the informed consent form is not dated for subjects [redacted]

C. The "Authorization to Release Information about Insurance Claims/Medical Records" forms for subjects [redacted] and [redacted] do not have the signature of a parent or legal guardian. This document was approved by the IRB to permit the sponsor to review medical records and insurance claims from September 1, 2000, through June 30, 2003. This form was a supplement to the informed consent document explaining the extent to which confidentiality of records identifying the subject would be maintained.

D. The informed consent form for subject 3 does not have the signature of the person obtaining consent, the signature of the witness other than the person obtaining informed consent, the child's name, or the date that the parent/legal guardian signed the informed consent. Additionally, the "Authorization to Release Information about Insurance Claims/Medical Records" form for subject 3 is not signed by the person conducting the consent interview.

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

A. You failed to complete the "Vaccine Accountability Log" for at least 36 shipments of investigational drug. The last entry in the "Vaccine Accountability Log" was 8/8/01, yet the last shipment was received 6/13/2002.

B. You failed to sign and date packing slips upon receipt, as required by the sponsor as part of the investigational plan [21 CFR § 312.60]. Examples include P0139250, P0139840, P0141868, P0140545, P0140835, P0151224, and P0152571. In addition, these packing slips do not describe the condition of the shipment at the time of receipt as required by the investigational plan.

Your response to the Form FDA 483 did not address these violations.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations, and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you believe you should remain eligible to receive 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:

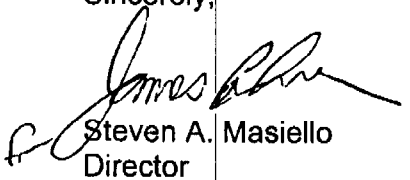
Steven A. Masiello, Director
Office of Compliance and Biologics Quality (HFM-600)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

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 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,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure: Proposed consent agreement

cc: Douglas B. Farquhar
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929