DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB - 4 2004

VIA OVERNIGHT MAIL

Notice of Opportunity for Hearing

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

Dear Dr. Daley:

The Food and Drug Administration (FDA, the agency) has information indicating that you repeatedly or deliberately violated federal regulations in your capacity as investigator in clinical trials with an unlicensed biological and investigational new drug, specifically, [redacted] vaccine. These violations provide the basis for the withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

By letter dated June 23, 2003, the Center for Biologics Evaluation and Research (CBER) informed you of the specific matters complained of and offered you an opportunity to explain them in writing or at an informal conference pursuant to § 312.70(a) of Title 21 of the Code of Federal Regulations (CFR). The letter also gave you the option of entering into a consent agreement with the agency, thereby terminating any administrative proceeding. You chose to respond in writing, in a letter dated August 15, 2003, transmitted through your attorney, [redacted] (August 15th explanation). CBER has concluded that your written explanations fail to adequately address the violations set forth below. Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR Part 16 and 312.70, on the question of whether you are entitled to receive investigational new drugs.

The allegations involve the following clinical study in which you are the clinical investigator of record: "Safety and Efficacy of [redacted] Vaccine in [redacted]

A listing of specific violations follows. Applicable provisions of the CFR are cited for each violation.

1. **You submitted false information to the sponsor [21 CFR §§ 312.62, 312.64 and 312.70].**

In your August 15th explanation, you do not deny that you submitted false reports to the study sponsor. Instead, you seek to excuse your conduct by arguing that accurate reports are not really important. For example, you state that it was not important to provide accurate information concerning when you administered vaccines, because "the only risk to patients would have been if the study vaccine was administered to the patient, and the administration of the vaccine were not recorded." August 15th explanation at 3. You ask FDA to rely on "[y]our understanding" concerning which patients actually received concomitant vaccines, and state that it is "unclear . . . why the listing of any dates different from the dates that the vaccines were actually administered has any material value in terms of the results." August 15th explanation at 3. Several times, you attempt to dismiss the significance of your false submissions, stating that the false statement or inaccurate record "would likely have no relevance" or "likely had no relevance." August 15th explanation at 3, 4 (twice). You ask FDA to excuse your failure to maintain and submit appropriate records because of the "confusion accompanying the large number of patients included as subjects in this clinical trial," August 15th explanation at 4, and because of an apparent unwillingness to adhere to "the rigors of observing all the technicalities of demanding and, in some cases, unnecessary protocol recordkeeping requirements." August 15th explanation at 5. You have not adequately explained these matters.

A. You submitted to the sponsor Case Report Forms (CRFs) containing false information 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 that Dose Was Falsely Represented to Have Been Administered	ID Number for Vial Falsely Represented to Have Been Administered
[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

In fact, these subjects never received the doses described. While you suggest possible explanations for why you might not administer vaccine doses, your explanation fails to explain why you affirmatively entered the vaccine vial ID number and date of vaccination for study vaccine/placebo that you did not administer, on that date or any other.

B. You submitted false information to the sponsor documenting the completion of post vaccination follow-up safety contacts for the subjects listed in item 1A, above – even though you never performed the safety contacts. 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. In fact, you never administered these vaccine/placebo doses to the study subjects, and you never performed follow up safety contacts. You submitted this information to the sponsor by facsimile transmission after the purported day 7 follow-up contact and in the CRFs for follow-up on days 7, 14, and 42. The following table lists the dates that you falsely reported that you completed follow-up safety contacts; this is not a complete list.

Subject	Date that Dose was Falsely Represented to Have Been Administered	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" signed by you and dated May 31, 2002, (which FDA obtained from related parties) you stated "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."

Your August 15th explanation does not dispute that you falsely documented that you conducted protocol-specified follow-up safety contacts when, in fact, you did not. Instead, you state, "Any failure to conduct follow-up contacts with Dr. Daley's patients would have been immaterial, since nearly all of the subjects who were enrolled in this study are regular patients of Dr. Daley; therefore patient contact was ongoing throughout the study." August 15th explanation at 3. Later, you state that the "vast majority of study subjects were regular patients of Dr. Daley." August 15th explanation at 7. You do not claim that you had contact with all of the patients, as the protocol required. You do not claim that you gathered the data required, at the times the protocol required. Any contact with regular patients that may have occurred did not satisfy protocol-specified requirements for telephone calls from your office to specifically request the subject's reaction 7, 14, and 42 days following each vaccination.

C. 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 that Dose was Falsely Represented to Have Been Administered	Week of Surveillance
[redacted]	1/02/02	6
	2/13/02	12
	3/27/02	18
	1/10/02	6
	2/21/02	12
	4/4/02	18
	12/5/01	6
	1/16/02	12
	2/27/02	18
	4/10/02	24
	1/12/02	6
	2/23/02	12
	4/6/02	18
	1/12/02	6
	2/23/02	12
	4/6/02	18
	1/12/02	6
	2/23/02	12
	4/6/02	18
	2/19/02	6

Subject	Date that Dose was Falsely Represented to Have Been Administered	Week of Surveillance
[redacted]	4/02/02	12
	1/13/02	6
	2/24/02	12
	4/7/02	18
	2/19/02	6
	4/02/02	12
	5/14/02	18
	4/06/02	6
	5/16/02	12
	4/18/02	6
	4/30/02	6
	4/30/02	6
	5/20/02	6
	6/11/02	12

Your August 15th explanation does not dispute that you falsely documented that you conducted protocol-specified follow-up safety contacts when, in fact, you did not. As we noted in section 1.B., you suggest that the regular patient contacts that Dr. Daley made with most subjects could be viewed as replacing the data gathering mandated by the investigational plan. However, any contact with regular patients that may have occurred did not satisfy protocol-specified requirements for telephone calls from your office to specifically request the subject's reaction 7, 14, and 42 days following each vaccination.

D. You reported in CRFs submitted to the sponsor that concomitant vaccines were administered to study subjects, when in fact no such vaccines were given on those dates. 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®. These concomitant 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 for eight subjects indicate that these subjects received concomitant vaccinations through local health clinics. Although the health clinic records are not included in your medical records for five of these subjects, you reported the administration of concomitant vaccinations to the sponsor. The health clinic vaccination records for the remaining three subjects do not contain concomitant vaccination information that is consistent with the data you reported in the CRFs. The following table is not a complete list.

Subject	Date of Administration Reported to Sponsor, but not Documented in Medical Records	Vaccine(s)
[redacted]	09/11/01	Hepatitis B, Prevnar®
	11/21/01	DTaP, IPV, Hib
	10/24/01	Hepatitis B, Prevnar®
	09/09/01	DTaP, IPV, Hib
	10/03/01	Hepatitis B, Prevnar®
	08/06/01	DTaP, IPV, Hib
	10/24/01	Hepatitis B, Prevnar®
	11/29/01	Hepatitis B, Prevnar®
	10/24/01	Hepatitis B, Prevnar®
	09/21/01	DTaP, IPV, Hib
	11/01/01	Prevnar®
	10/24/01	DTaP, IPV, Hib
	10/24/01	DTaP, IPV, Hib
	01/08/02	Hepatitis B, Prevnar®
	12/02/01	Hepatitis B, Prevnar®
	11/21/01	DTaP, IPV, Hib
	01/08/02	Hepatitis B, Prevnar®
	12/14/01	Hepatitis B, Prevnar®
	10/11/01	Prevnar®
	12/18/01	Prevnar®
	10/25/01	Prevnar®
	02/21/02	Hepatitis B, Prevnar®
	02/01/02	DTaP, IPV, Hib
	04/17/02	Hepatitis B
	02/21/01	DTaP, IPV, Hib
	03/19/02	Hepatitis B, Prevnar®
	04/08/02	Hepatitis B, Prevnar®
	03/07/02	DTaP, IPV, Hib
	04/10/02	DTaP, IPV, Hib
	03/27/02	DTaP, IPV, Hib
	05/06/02	Hepatitis B, Prevnar®
	04/24/02	Prevnar®

Your August 15th explanation states, "It is our understanding that all of the study subjects received the concomitant vaccines that were listed in patient records as having been administered. It is unclear, therefore, why the listing of dates different from the dates that the vaccines were actually administered has any material value in terms of the results collected for the clinical study." August 15th explanation at 3.

However, the sponsor required the correct date of concomitant vaccination administration for the "Concomitant Non-Study Vaccine" CRFs for Vaccination Visit Follow-Up for Visits 1,2, and 3. These CRFs require the reporting of concomitant vaccines that were received by study subjects during the 42 days of the protocol specified follow-up period. You did not document the vaccination dates listed in this table in the subjects' medical records, yet you told the sponsor that you administered these concomitant vaccinations to infant subjects on these dates.

E. The protocol defines a serious adverse event (SAE) as an event that, among other things, "results in or prolongs an existing inpatient hospitalization." You submitted false information to the sponsor regarding the absence of SAEs. 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. In fact, 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.

F. You wrote the word "rectal" instead of "underarm" 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 told the FDA investigators that you had, 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).

In your August 15th explanation, you state "the listing of rectal temperatures, converted from temperatures under the arm, would only have been a material misstatement if the study subject had a fever." You further suggest that taking a temperature is not necessary to determine whether a study subject suffered a fever, and that "human touch" would be adequate for this purpose. August 15th explanation at 3-4. We disagree. Moreover, the CRF contained a space labeled "method" for the entry of the method utilized to obtain the subject's temperature. Your explanation fails to explain why "rectal" was entered as the "method" of temperature collection when this was an incorrect statement.

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

A. Protocol section I.G requires follow-up for adverse experiences at days 7, 14, and 42 after each vaccine/placebo dose, and that the presence or absence of adverse experiences be documented on CRFs. You failed to document the occurrence and follow-up of 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.

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 had 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 12/31/01 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 had 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 "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?"

In your August 15th explanation, you attempt to dismiss these reporting failures as "likely" to be insignificant. You note that subjects [redacted] and [redacted] did not have [redacted] and you concluded that the subjects' hospitalization "likely had no relevance to other principal investigators or to the IRB monitoring the study." August 15th explanation at 4. However, as a clinical investigator participating in the study, you were responsible for the complete and accurate reporting of serious adverse events to the sponsor in accordance with the protocol.

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 That Dose Represented to Have Been Administered
[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

Subject	Dose	Date That Dose Represented to Have Been Administered
[redacted]	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

In your August 15th explanation, you only offer explanations for why you might not have administered the vaccine doses. You do not explain why you created false records concerning a vaccine vial ID number and date on which you falsely claimed to have administered the vaccine/placebo.

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 claimed to have administered, but did not 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, in reality, were not given to the subjects.

In your August 15th explanation, you fail to address why you (1) removed the labels from unadministered vials of study vaccine, (2) affixed these vial labels in the "Vaccine Inventory and Label Log," (3) falsely recorded a date on which you purportedly administered the vaccine, (4) falsely recorded an amount of vaccine purportedly administered, and (5) falsely named another individual as the administrator of vaccine.

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 That Dose Represented to Have Been Administered	Date Day 7 Safety Contact Represented to Have Occurred	Date Day 14 Safety Contact Represented to Have Occurred	Date Day 42 Safety Contact Represented to Have Occurred
[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

In your August 15th explanation, you state "Any failure to conduct follow-up contacts with Dr. Daley's patients would have been immaterial since nearly all of the subjects who were enrolled in this study are regular patients of Dr. Daley." August 15th explanation at 3. You do not claim that you had contact with all of the patients, as the protocol required. Moreover, any contact with regular patients that may have occurred did not satisfy requirements to prepare and maintain complete and accurate study records. Your explanation does not dispute that your recorded that you had performed follow-up safety contacts, when, in fact, you had not.

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 Represented to Have Been Administered	Vaccine(s)
[redacted]	06/21/01	Hepatitis B, Prevnar®
	08/23/01	Hepatitis B, Prevnar®
	09/24/01	DTaP, IPV, Hib
	09/11/01	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
	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 report the administration of concomitant vaccines that, according to subjects' medical records, you did administer. Examples include the following:

Subject	Date Medical Record Shows Vaccine(s) Administered	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®
	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]

The subjects listed in Tables E.i and E.ii represent a significant number of subjects enrolled in the trial. Your August 15th explanation fails to explain why you did not accurately report the administration of concomitant vaccinations to the infants in this study.

F. 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] through [redacted] received 3 doses of vaccine/placebo, for a total of 27 doses, and the SVARs show that subject [redacted] received two vaccine/placebo doses and that subjects [redacted] through [redacted] received a single vaccine/placebo dose, for a total of 10 doses.

Attempting to address these deficiencies, your August 15th explanation refers to "the technicalities of demanding and, in some cases, unnecessary protocol recordkeeping requirements." August 15th explanation at 5. When you signed the Form FDA 1572 for this study, you agreed to follow the requirements of the protocol and to follow FDA regulations. You should have terminated your participation as soon as you realized you were not capable of honoring this responsibility and commitment.

G. 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]

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.

In your letter to FDA dated September 20, 2002, responding to the inspection, and your August 15th explanation, you state that because you were the only clinical investigator at the site and you know your patients well, it was not critical to maintain the "Study Participation Log." Once again, your only response is to dismiss the importance of the rules that you explicitly agreed to follow when you assumed the role of investigator.

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.

In your August 15th explanation you attempt to diminish the significance of these events, "Given that the primary goal of the study was to uncover any instances of [redacted] the subject's hospitalization would likely have no relevance to other principal investigators or to the Institutional Review Board (IRB) monitoring the study." August 15th explanation at 4. Once again, you simply dismiss the importance of the rules that you explicitly agreed to follow when you assumed the role of investigator.

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 with [redacted] You failed to collect [redacted] specimens from subjects who were hospitalized with symptoms of [redacted]

Your August 15th explanation addresses a [redacted] collected from a third subject but does not explain why [redacted] samples were not collected from the two subjects in question.

D. 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] Subject [redacted] had [redacted] and had been treated with [redacted] You administered the first dose of study vaccine/placebo to Subject [redacted] on 6/12/01 before you obtained the sponsor's waiver on 6/13/01 permitting you to enroll this ineligible subject. Furthermore, you falsely recorded "No" for the presence of this condition on the subject's case report form.

In your August 15th explanation, you state that the sponsor orally granted permission to administer study vaccine to subject [redacted] prior to the actual administration. You state "documents in the subjects' [sic] CRFs confirm that the sponsor's medical monitor approved the waivers at about the time the vaccine was administered." August 15th explanation at 6. You did not provide copies of the documentation that supports your statement.

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

i. You failed to report to the IRB that subjects [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 [redacted] subject [redacted] was hospitalized because the [redacted] was not resolved. A letter from the sponsor dated 1/24/02 reminded you, "Please notify the ERC [IRB] of this SAE."

In your August 15th explanation, you state that subjects [redacted] and [redacted] did not have [redacted] and concluded that the hospitalization of these subjects "likely had no relevance to other principal investigators or to the IRB monitoring the study." August 15th explanation at 4. Once again, your only response is to claim that your failure "likely" was unimportant.

B. On April 2, 2002 and April 17, 2002, you applied for continuing review of the study, but falsely advised the IRB that no subjects had experienced SAEs. In fact, by April 2, 2002, subjects [redacted] had experienced SAEs. 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 this form to the IRB, however, your response to this question still remained "NO."

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

Your August 15th explanation provides no explanation and simply contends this violation is "truly immaterial." August 15th explanation at 6.

D. 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." One hundred ninety six of the two hundred sixty four 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 appearing on the informed consent forms. She 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] appears identical to the handwriting style of the name [redacted] on the informed consent forms of 195 additional study subjects.

In your August 15th explanation you state, "there is no question that [redacted] generally did witness or confirm with signatories that they had signed the informed consent forms." August 15th explanation at 6. This, of course, does not explain why [redacted] name was signed as a witness on the consent form, without her consent.

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 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.

Your August 15th explanation does not specifically address this violation.

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 6/13/02.

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.

You have not explained these violations, but simply dismiss them as "relatively unimportant and relatively common." August 15th explanation at 7.

Pursuant to 21 CFR §§ 16.22 and 312.70(a), you are hereby notified of your opportunity for a regulatory hearing before FDA to determine whether you should be disqualified from receiving investigational drugs. The matters to be considered at the hearing are set forth in paragraphs 1 through 6, above. Under FDA regulations, you have the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in Title 21 of the Code of Federal Regulations, Part 16, and the FDA's guidelines on electronic media coverage of public administrative proceedings, 21 CFR § 10, Subpart C. Copies of those regulations are enclosed.

Your written request for a hearing must be postmarked, if mailed, or received, if faxed (with the original to follow by mail), within ten (10) working days of receipt of this letter. Please address the letter to:

Dr. James F. McCormack
Division of Compliance Policy (HFC-230)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
Telephone (301) 827-0425
Facsimile (301) 827-0482

If no response to this letter is received by that time, you will be deemed to have waived your right to a regulatory hearing, and a decision in this matter will be made based on the facts available to the agency.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR § 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact has been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Dr. McCormack within the time period specified above and send a written response containing your reply. The letter should state that you waive your right to a hearing and that you want a decision on the matter to be based on your written response and other information available to the agency.

The agency's offer to enter into a consent agreement remains open. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding. You were sent a draft consent agreement enclosed with FDA's letter to you dated June 23, 2003. If you would like to choose this option, please contact Dr. McCormack.

No final decision by FDA has been made at this time on your eligibility to continue to use investigational drugs. Moreover, there will be no prejudgment of this matter if you decline to enter into a consent agreement and decide instead either to request a regulatory hearing or to request that the decision be based on information currently available to the agency.

Please inform Dr. McCormack within ten (10) working days whether you wish to request a hearing or to have this matter resolved by consent agreement or based on the information available to the agency.

Sincerely yours,

John M. Taylor, III
Associate Commissioner for
Regulatory Affairs

Enclosures
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 312

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