



[Home](#) > [Inspections, Compliance, Enforcement, and Criminal Investigations](#) > [Enforcement Actions](#) > [Warning Letters](#)

Inspections, Compliance, Enforcement, and Criminal Investigations

Toledo, Charles H., M.D. 3/11/10



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville, MD 20852-1448

March 11, 2010

By Facsimile Transmission and Overnight Delivery

CBER-10-05

Charles H. Toledo, M.D.
Western North Carolina Pediatric and Adolescent Care
293 Hospital Road, Suite D
Sylva, North Carolina 28779

Warning Letter

Dear Dr. Toledo:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted between August 3, 2009, and September 30, 2009. An FDA investigator met with you to review your conduct of the following clinical studies:

(b)(4)

This inspection was conducted as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational drugs.

At the end of the inspection conduct at Sylva Pediatric Associates, the FDA investigator contacted you and met with you to discuss the items listed on the Form FDA 483, Inspectional Observations. You responded to the Form FDA 483 in a letter to the Atlanta District Office dated October 22, 2009. We reviewed the inspection report, the supporting documents submitted with that report, and your October 22, 2009 letter.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR) Part 312 (available at <http://www.gpoaccess.gov/cfr/index.html>).

The applicable provisions of the CFR are cited for each violation listed below.

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations in order to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60].

Study 1

A. Section 8.5 of the protocol requires that all adverse events" occurring within 31 days (Days 0-30) following administration of each dose of study vaccine must be recorded on the 'Adverse Event' form in the subject's eCRF, irrespective of severity or whether or not they are considered related to vaccination."

The following adverse events were not reported to the sponsor in the subjects' electronic Case Report Form (eCRF).

Subject	Adverse Event(s)	Date
(b)(6)	Vomiting, diarrhea, fever	02/02/04
(b)(6)	Scabies	11/11/04
(b)(6)	Bilateral otitis media	03/21/06
(b)(6)	Dots/rash on arms, legs, trunk, face	11/12/05
(b)(6)	Right otitis media	12/01/05
(b)(6)	Left otitis media	06/27/05

B. Section 8.5 of the protocol specifies that "All new onset chronic illnesses and other medically significant events occurring during the Active Phase and the Extended Safety Follow-up Phase must also be reported." The following events were not reported in the eCRFs.

Subject	Adverse Event(s)	Date
(b)(6)	Seizure with fever	03/13/05
(b)(6)	Febrile seizure	06/08/05
(b)(6)	Admitted to ER unconscious	12/14/05

C. Protocol Section 6.9 requires that "All concomitant medications, with the exception of vitamins or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine(s) and ending 42 days following the first dose of study vaccine(s) and 31 days following subsequent doses of study vaccine are to be recorded..." The following concomitant medications were not reported to the sponsor in the eCRF for the following subjects:

Subject	Concomitant Medication	Date	Date of Last Study Vaccine
(b)(6)	Phenergan	2/204	1/6/04
(b)(6)	Permethrin cream	11/11/04	11/11/04
(b)(6)	Triaminic	5/24/04	4/27/04
(b)(6)	Augmentin and Ciprodex	3/21/06	2/20/06
(b)(6)	Omnicef	12/1/05	11/8/05
(b)(6)	Omnicef	6/27/06	5/30/06

D. Section 9.2.1 of the protocol requires that "Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up." Source documents for Subject (b)(6) show that this subject dropped from the study after Visit 2 on November 15, 2005. An attempt to contact this subject did not occur until a phone call on August 17, 2006. The phone call is documented in the subject's medical record and confirms that the subject dropped from the study after Visit 2. Subject (b)(6) did not return for Visits 3, 4, or 5.

E. Protocol Section 4.4 describes elimination criteria during the study and includes "Administration of a vaccine not foreseen by the study protocol during the study period starting from 31 days before each dose of study vaccine(s) and ending 31 days after". Subject (b)(6) received a study vaccine on October 22, 2004 and an influenza vaccine on November 10, 2004. Although Subject (b)(6) met the elimination criterion this subject was continued in the study.

Study 2

The "Investigational Product Dispensing and Reconciliation Form" and the "Delegation of Authority Log" show that study vaccines were administered by individuals not authorized to dispense the study vaccine.

Subject	Date	Dispenser Initials
(b)(6)	07/18/07	(b)(6)
(b)(6)	11/13/07	(b)(6)
(b)(6)	11/13/07	(b)(6)

In your letter, you explain that you do not have access to the records for Studies 1 and 2.

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

Study 1

A. Adverse events the onset of new medically significant events, and concomitant medications recorded in subjects' medical records were not reported in the subjects' eCRFs. Refer to Item 1 A, B, and C.

B. Discrepancies were observed between source documents and eCRFs, the "Investigational Product(s) Dispensing Record," and the "Investigational Product Accountability and Reconciliation" Records as described in Item 3.

C. Protocol section 4.4 describes elimination criteria during the study and includes "Administration of a vaccine not foreseen by the study protocol during the study period starting from 31 days before each dose of study vaccine(s) and ending 31 days after". Subject **(b)(6)** received a study vaccine on October 22, 2004 and an influenza vaccine on November 10, 2004. This elimination criterion was not reported in the subject's eCRF until July 22, 2008.

Study 2

D. The following discrepancies were noted between source documents and eCRFs in Study 2:

- i. Subject **(b)(6)** received a **(b)(4)** vaccination as part of the study protocol on November 13, 2007. On November 23, 2007 this subject was diagnosed with "**(b)(4)**, vaccine induced". The eCRF reported this occurrence to the sponsor as "**(b)(4)**" and failed to inform the sponsor that the subject developed vaccine induced **(b)(4)**.
- ii. The "Serious Adverse Event Reporting Form" for subject shows a diagnosis of reactive airway disease and wet cough beginning December 21, 2007 and December 24, 2007, respectively. However, the chest x-ray reports perihilar viral pneumonia for this subject.

In your letter, you explain that you do not have access to the records for these studies.

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

The following discrepancies were observed between source documents and eCRFs, the "Investigational Product(s) Dispensing Record", and the "Investigational Product Accountability and Reconciliation" Records in Study 1:

Subject	Vaccines Administered per Source Document and eCRF	Investigational Product(s) Dispensing Record	Investigational Product Accountability and Reconciliation
(b)(6)	(b)(4) on 1/8/04 and 7/21/04	(b)(4) on 1/8/04 and 7/21/04	4 empty vials returned
(b)(6)	(b)(4) and (b)(4) on 3/8/04	(b)(4) on 1/8/04 and 7/21/04	4 empty vials returned
(b)(6)	(b)(4) on 5/4/04; (b)(4) and (b)(4) on 3/22/04	(b)(4) on 5/4/04; (b)(4) and (b)(4) on 3/22/04	4 empty vials returned
(b)(6)	No vaccinations due to withdrawal of consent	No record found	4 empty vials returned
(b)(6)	No vaccinations due to withdrawal of consent	No record found	4 empty vials returned
(b)(6)	(b)(4) on 11/10/05 and 5/30/06	(b)(4) on 5/30/06	10/12/04: Returned due to expiration; Not replaced

In your letter, you explain that you do not have access to the records for this study.

4. You failed to retain records required to be maintained for a period of two years following the date a marketing application is approved for the indication for which the drug is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued. [21 CFR § 312.62(c)].

At the time you signed the Form FDA 1572, Statement of Investigator, for Studies 1 and 2, you agreed to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make these records available for inspection in accordance with 21 CFR 312.68. In your letter, you explain that you do not have access to the study record because your affiliation with Sylva Pediatric Associates (SPA) ended in **(b)(6)**. Our investigation revealed that after your departure from Sylva Pediatrics records of your completed studies were stored by **(b)(4)**. After **(b)(4)** closed, your records were relocated to SPA and did not remain under your supervision at your current position at Western North Carolina Pediatric and Adolescent Care in Sylva, North Carolina.

Because you do not have access to the study records, your response to many of the items cited on the Form

FDA 483 in your letter is "To the best of my knowledge without access to the study records this must have been transcription/human error." This response is not adequate, because FDA's regulations require you, as an investigator, to retain these records for two years after the date a marketing application is approved for the indication for which the drug is being investigated or for two years after the discontinuation of the study if no marketing application is filed and approved by the FDA.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational vaccines. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

In your letter, you described a corrective action plan for future trials that included work practice guides, flow charts, and additional training of study personnel. We request that you explain your corrective action plan for maintaining study records in the future.

Within fifteen (15) business days of receipt of this letter, please provide written documentation of the actions you will take to correct these violations and prevent the recurrence of similar violations in current and future studies for which you are the clinical investigator. Failure to respond to this letter and to take appropriate corrective action could result in FDA taking regulatory action without further notice to you. FDA could initiate disqualification proceedings against you in accordance with 21 CFR 312.70.

Please send your written response to:

Christine Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1488
Telephone: 301-827-6323

We also request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

/S/

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

cc:

John Gridley, District Director
60 Eighth Street NE
Atlanta, Georgia 30309

Links on this page: