

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date May 13, 2010

From Solomon Yimam, Bioresearch Monitoring, HFM-664
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality

Through Patricia Holobaugh, Bioresearch Monitoring Branch Chief, HFM 664

To Chair BLA Committee

File BLA 125363/0

Product: MenHibrix™ [Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine]

Indication Active immunization against Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y in infants.

Subject Summary of Bioresearch Monitoring Inspections

Sponsor GlaxoSmithKline Biologicals

SUMMARY STATEMENT

Four Bioresearch monitoring inspections were conducted in support of BLA 125363/0. Of these, three were clinical investigators and one was the sponsor's laboratory that performed the immunogenicity assays. The bioresearch monitoring inspections did not reveal problems that impact the data submitted in the application.

BACKGROUND

The BIMO data audit inspection for this BLA focused on protocol HiB-MenCY-TT 009/010 study as well as the sponsor's laboratory that performed the immunogenicity assays. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The BIMO inspection assignment included specific questions for the following study:

- A Phase III, randomized, multinational study, double-blinded for the immunogenicity and consistency evaluation of 3 Hib-MenCY-TT vaccine lots and single-blinded and controlled for the evaluation of safety and immunogenicity of GSK Biologicals' Haemophilus influenza type b and Neisseria meningitides serogroups C and Y –tetanus toxoid conjugate vaccine combined (Hib-MenCY-TT) compared to monovalent Hib vaccine in healthy infants at 2, 4, 6, and 12 to 15 months of age.*

CENTER #	STUDY SITE	LOCATION	NUMBER OF SUBJECTS	FORM FDA 483 ISSUED	FINAL CLASSIFICATION
24658	Pediatric Associates	Falls River, Massachusetts	133	NO	NAI
19895	Palmeto Pediatrics	Charleston, South Carolina	288	NO	NAI
19848	Wee Care Pediatrics	Layton, Utah	270	YES	VAI
	GSK Clinical Laboratory	Rixensart, Belgium		NO	NAI

NAI – No Action Indicated, VAI – Voluntary Action Indicated, EIR – Establishment Inspection Report

INSPECTIONAL FINDINGS

One of the 4 inspections documented numerous concerns with the conduct of the study. The observations for center 19848 are as follows:

- 1. Failure to ensure that the investigation was conducted according to the investigational plan, the signed investigator statement, and applicable FDA regulations [21 CFR § 312.60].**

 - a. Subject # 647-35424 of Cohort 2 was administered regular six-month clinic vaccines instead of study vaccines at Visit 3 on 9/5/06.
 - b. Subjects 000662 and 000665 were assigned to the randomization numbers 35901 and 36120 from the Hib-MenCY-TT. However, the subjects were administered with the doses for randomization numbers 36201 and 36210, later revealed to be Monovalent Hib group, at visit 2.
 - c. For subjects in cohort 1, the protocol requires a minimum of 5.0 mL of whole blood drawn at Visit 4 and at pre-vaccination at Visit 5. However, Subject 775-31217 had only 2 mL of blood drawn at Visit 4 and no blood was collected from subject 800-30558 prior to the administration of the booster vaccine on 10/8/2007, at Visit 5.
 - d. The protocol requires the study personnel to contact subjects' parents/guardians in cohort 1, 42 to 56 days after Visit 5 and for cohort 2 subjects, 31 to 37 days after Visit 5. Nevertheless, review of following subjects' files revealed the protocol specified time frame was not met:

Subject #	Cohort	Visit # 5	Telephone Follow-up date
773/31179	1	9/7/07	12/12/07
700/36127	2	4/9/07	7/9/07
708//36445	2	6/27/07	9/6/07
9047/36455	2	7/6/07	9/6/07

- e. Section 5.5 of the protocol requires study personnel to contact the subjects' parents or guardians within day 1 to day 3 post vaccinations, but the following subjects were not contacted within the specified time frame.

Subject #	Visit #	Date	Telephone Follow-up Date
9047/36455	5	7-06-07	None
679/36109	1	5-30-06	6-05-06
679/36109	2	7-27-06	8-02-06
679/36109	5	4-13-07	4-23-07
688/36206	5	4-10-07	4-17-07

2. Failure 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)].

- a. There was no documentation to show that subject 661-35899 observed closely for thirty minutes following the administration of the vaccine at visit 2, as specified in the protocol.
- b. Subject 679-36109 had a fever reported on Day 1 after the Visit 1 vaccination, but the adverse event was not documented in the subject's source document.
- c. There was no documentation to show that the elimination criteria was evaluated for subject 793-31257 for Visit 5 on October 1, 2007.
- d. Discrepancies were noted between the weights documented in the source document and the CRF for subject 688-36206 at Visit 5. The 4/10/07 source document shows the subject's weight as 19 lbs 14 oz, but the CRF shows the subject's weight as 10 lbs 10 oz.
- e. The source documents for subject 775-31217 document that the subject withdrew from the study after Visit 5, but there is no reason for the withdrawal and no date of last contact documented in the source documents.

3. Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR § 312.62(a)].

- a. Discrepancies were noted in the investigational Product Accountability and Reconciliation records dated 5/22/07, 6/20/07, and 6/21/07. For example,

the final disposition of test article, diluent, and concomitant vaccines were not adequately and consistently maintained.

- b. The booster vaccine records for subjects in Cohort 1 were missing. During the inspection, a study team member created the investigational product dispensing and reconciliation form by gathering information contained in the subjects files in cohort 1.
- c. There were no records of the receipt of the drugs for 9 of the 192 randomization records reviewed. Study drugs were transferred from another clinic for randomization numbers 30557, 30561, 30562, 30563, 30564, 60109, 60110, 60111, and 30112. As noted, during the inspection a study staff stated that the drugs were transferred from another clinic, but there was no record of the transfer.

SPONSOR ISSUES

No sponsor or monitoring issues were noted.

SPONSOR'S TESTING LABORATORY

The inspection revealed no deviations from applicable federal regulations.

FINANCIAL DISCLOSURE

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children, and if and when the information was updated. All inspected sites had copies of the financial disclosure forms for the clinical investigators and sub-investigators.

BIMO ADMINISTRATIVE FOLLOW-UP

CBER BIMO issued letters that describe the inspection results to centers 19848 and 24658. Correspondence will be issued to Study Site 19895 and the sponsor's laboratory after complete review of the establishment inspection reports and final classification. Should you have any questions about this memorandum please contact me at (301) 827-1948.

Solomon Yimam
Consumer Safety Officer