

# Summary of Bioresearch Monitoring Inspection - Cervarix, September 5, 2008

## MEMORANDUM

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

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**DATE** September 5, 2008

**FROM** Solomon Yimam, Bioresearch Monitoring, HFM-664

Division of Inspections and Surveillance

Office of Compliance and Biologics Quality

**SUBJECT** Summary of Bioresearch Monitoring Inspection

BLA 125259/0

**SPONSOR** GlaxoSmithKline

2301 Renaissance Boulevard

P.O.Box 61540

King of Prussia, Pennsylvania 19406-2772

**PRODUCT** Cervarix <sup>TM</sup> (human papillomavirus vaccine)

**THROUGH** Patricia Holobaugh, Bioresearch Monitoring Branch Chief, HFM 664

**TO** Robin Levis , HFM-451

### Summary

The bioresearch monitoring inspections of three clinical sites did not reveal problems that impact the data submitted in the application.

### BACKGROUND

Inspections of four clinical investigators were requested in support of the BLA and 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 in the study entitled *A phase III, double-blind, randomized, controlled, multi-center study to evaluate the efficacy of GlaxoSmithKline Biologicals' HPV-16/18 VLP AS04 vaccine compared to hepatitis A vaccine as control in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy females 15-25 years of age (HPV-008)* . The assignment included instructions to compare data from the BLA and the source documents and to verify and answer questions regarding the study.

Center # Location

#of Subjects enrolled Form FDA 483 Issued Final Classification

4924 Philadelphia , Pennsylvania 126

Yes

VAI

Center # Location		#of Subjects enrolled Form FDA 483 Issued Final Classification		
4951	Bardstown , Kentucky	159	Yes	VAI
4929	Albuquerque , New Mexico	510	No	NAI
4923	Salt Lake City , Utah	21	Yes	VAI

## INSPECTIONAL FINDINGS

1. Failure to ensure that an investigation is conducted according to the investigational plan. [21 CFR § 312.60].
  - a. Repeat cervical cytologies were not performed for 12 Subjects at the next scheduled visits as specified in the algorithm. (center 4951)
  - b. The algorithm-required follow-up colposcopy evaluations were not performed for Subjects 3165, 2286, 2267, and 3151. (center 4951)
  - c. According to "The Source Document Worksheet" a visit must be rescheduled if the response for question number 2 is "yes", but one Subject was administered the third dose of the study vaccine during visit number 3 even though the response to question number 2 about recent sexual activity was marked "yes". (center 4951)
  - d. The protocol requires suspension of cervical exams and collection of cervical specimen for three months until a pregnancy has ended, but the protocol was not followed for Subject 3164 at visit 6 month18. (center 4951)
  - e. Blood samples were not obtained at visit #3 (6 months) for 17 subjects. (center 4951)
  - f. Subject 2249 received investigational drug assigned to subject 2248 at visit #3. (center 4951)
  - g. Subject 2235 received live vaccine (FluMist) within 30 days of the study drug administration. (center 4951)
  - h. Center 4924 had Delays in reporting Serious Adverse Events to the sponsor within 24 hours as specified in the protocol.
  - i. 15 of the 162 screened Subjects did not sign in the subject's signature line on the subjects screening form. (Center 4924)

### Center 4923 inspection

In a letter dated 02-27-2007, the sponsor notified FDA of Good Clinical Practices violations. The complaint alleged that center 4923 was terminated from participation in this protocol due to lack of adequate clinical investigator oversight and failure to conduct the study according to the investigational plan and the signed agreement.

During the period from 7/2/04 to 11/7/06, the sponsor conducted 21 monitoring visits at center 4923. The monitoring visits prior to October 2006 did not reveal problems with the conduct of the study, but the October and November 2006 monitoring visits identified issues in conduct of the study.

BIMO issued a complaint inspection assignment for the Denver District Office to conduct a directed inspection of the Center. The inspection was conducted from 10/10/2007 to 10/24/2007. During the inspection, we learned that the center was no longer affiliated with the Contract Research Organization (CRO) where the studies were conducted.

The inspection documented numerous concerns with the conduct of the study. At the conclusion of the inspection, a Form FDA 483, Inspectional Observations was issued. An Untitled Letter with following observations was issued on May 22, 2008:

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

#### **SPONSOR ISSUES**

Monthly monitoring visits were conducted at center 4951, but the monitors did not identify the center's non-compliance with the protocol required cytology and colposcopy algorithms.

#### **BIMO ADMINISTRATIVE FOLLOW-UP**

We issued letters that describe the inspection results to the four clinical investigators. Should you have any questions about this memorandum please contact me at (301) 827-1948.

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Solomon Yimam  
Consumer Safety Officer