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

DATE December 2, 2014

FROM Erin McDowell, Bioresearch Monitoring Branch
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality

THROUGH Patricia Holobaugh, Chief, Bioresearch Monitoring Branch

THROUGH Gilliam Conley, Director, Division of Inspections and Surveillance

TO Haruhiko Murata, BLA Committee Chair
Sixun Yang and Nancy Miller, Clinical Reviewers
Laura Montague and Bharat Khurana, RPMs

SUBJECT Bioresearch Monitoring Discipline Review Memo Addendum
BLA: STN 125508/0
IND: 13447
PRODUCT: 9-valent HPV vaccine (Gardasil-9)
SPONSOR: Merck & Co., Inc.

REVIEW SUMMARY

Bioresearch Monitoring inspections of six clinical investigators were conducted in support of this Biologics Licensing Application (BLA). Inspections of these clinical investigators did not reveal significant problems that impact the data submitted in this BLA.

BACKGROUND

Six clinical sites covering two pivotal studies were proposed for inspection by the Bioresearch Monitoring Branch member of the review committee. The review committee concurred with the proposed sites. The clinical sites were selected based on the number of subjects' enrolled, previous inspectional history, conduct of two of the pivotal studies, financial disclosure, and geographic location.

STUDY TITLES

A Randomized, International, Double-Blinded (With In-House Blinding), Controlled With GARDASIL™, Dose-Ranging, Tolerability, Immunogenicity, and Efficacy Study of a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine Administered to 16- to 26-Year-Old Women. [**Protocol No. V503-001**; **NCT00543543]**

A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds) [**Protocol No. V503-002**; **NCT00943722**]

Subjects were enrolled at 28 United States sites and 77 sites outside of the United States for study V503-001. Three of the five sites selected for inspection are located in the United States and two sites are located outside of the United States. The five selected sites inspected for study V503-001 represent 4.7% of the clinical study sites that enrolled subjects. The number of subjects enrolled at the five selected inspection sites selected for data verification represented 9% of the total subjects enrolled in the study.

Subjects were enrolled at 21 United States sites and 51 sites outside of the United States for study V503-002. Two of the three sites selected for inspection are located in the United States and one site was located outside of the United States. The three selected sites inspected for study V503-002 represent 4% of the clinical study sites that enrolled subjects. The number of subjects enrolled at the five selected inspection sites selected for data verification represented 6.8% of the total subjects enrolled in the study.

The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. Information submitted in the BLA was compared to source documents at each clinical site. The inspection assignment included specific questions concerning the clinical study.

INSPECTION SITES:

Bioresearch Monitoring inspections were conducted at the following clinical sites:

Study	#Subjects	Site#	Study Site	Location	Form FDA 483 Issued	Final Classification
V503-001 V503-002	105 26	001-0005 & 001-0106 002-17	Georgia Regents University Research & Medical College of Georgia Research	Augusta, Georgia	No	**NAI**
V503-001	113	001-0006	H. Lee Moffitt Cancer Center and Research Institute	Tampa, Florida	No	**NAI**
V503-001	139	001-0008	University of Washington	Seattle, Washington	Yes	**VAI**
V503-002	55 total	V002-24, V002-47, V002-49,	Primary Physicians Research Inc. (transferred to Preferred Primary Care Physicians, Inc.)	Carnegie Pennsylvania	No. CI change for extension study; Deficiencies identified for original site.	**NAI**
V503-001 V503-002	135 130	001-0035 002-04	Vaccine Trial Center, Faculty of Tropical Medicine Mahidol University	Bangkok Thailand	Yes	**VAI**
V503-001	953	001-0027	Frederiksberg Hospital	Frederiksberg Denmark	Yes	**VAI**

NAI=No Actions Indicated; VAI=Voluntary Action Indicated

No Form FDA 483s were issued to the sites in Augusta, Georgia and Tampa, Florida. The final inspection classification for the clinic sites in Tampa, Florida; Augusta, Georgia; and Carnegie, Pennsylvania are NAI (No Action Indicated).

The Carnegie, Pennsylvania site had no deficiencies identified for the extension portion of the study. For the portion of the study conducted by a former clinical investigator, several deficiencies were identified including failure to maintain study records for three subjects, failure to report to the sponsor one subject who was administered an extra dose of HPV vaccine, one instance of a mix-up of vaccine doses, and failure to maintain IRB and temperature monitoring records.

A three-item Form FDA 483 was issued to the site in Seattle, Washington. Items listed on the 483 included incomplete informed consent forms for minors enrolled in the trial, lack of verification of subject age, and missing vital sign documentation for over 10 subjects for 1-3 study visits.

The BIMO inspection at the Denmark site revealed that the investigator took over for another investigator in June 2010 and was the clinical investigator for a total of 3 sites. Each site had a delegated sub investigator to perform the normal duties of the clinical investigator. A 1 item 483 was issued to the site for enrolling a 17 year old (the IEC approved the study for females 18 years and older). Several oversights were noted for the original investigator but were not listed on the Form FDA 483 since the original investigator had retired.

The BIMO inspection of the Thailand site revealed several minor discrepancies between the case report form and source documents. Corrections were issued for these discrepancies in response to the 483.

In addition to the original submission for BLA 125508/0, the BIMO review included, but was not limited to, the following:

Information Request # & date	**Response in BLA Amendment #**	**Submission Date**
IR #1, dated Feb. 14, 2035	125508/0/4	14-Mar-14
IR#2, dated Mar. 12, 2014	125508/0/6	28-Mar-2014
IR #3, dated Mar. 21, 2014	125508/0/7	28-Mar-2014 (Letter date 1-Apr-14)
IR#5, dated Apr. 23, 2013	125508/0/13	12-May-14

SPONSOR ISSUES

No sponsor or monitoring issues were noted at the sites that were inspected.

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. The information submitted to the BLA was verified for each of the inspected clinical sites.

ADMINISTRATIVE FOLLOW-UP:

Information letters were issued to six clinical investigators.

Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at (240) 402-9140.

Erin McDowell
Consumer Safety Officer