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

DATE February 18, 2015

FROM Dennis T. Cato, Bioresearch Monitoring Branch
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THROUGH Patricia Holobaugh, Chief, Bioresearch Monitoring Branch

THROUGH Gilliam Conley, Director, Division of Inspections and Surveillance

TO

Matthew Steele	Chair, Review Committee
Juan Lacayo	RPM
Scott Norris	RPM
Sarah Browne	Clinical Reviewer

SUBJECT Bioresearch Monitoring Addendum to the Discipline Review Memo

BLA/STN:	125525/0
IND:	14668
Sponsor:	Sanofi Pasteur Inc.
Product:	Diphtheria-Tetanus-Pertussis-Polio Vaccine (QUADRACEL)

REVIEW SUMMARY

Bioresearch Monitoring (BIMO) inspections assignments were issued for 3 clinical investigators and 4 domestic clinical investigator study sites. All inspections have been completed and the inspection reports were reviewed and the inspections classified, and the Establishment Inspection Reports (EIRs) for the completed inspections did not reveal problems that impact the data submitted in this biologics licensing application (BLA).

BACKGROUND

Clinical Investigator Inspection Assignments were issued for 3 clinical investigators and 4 domestic clinical study sites in support of this BLA. The 4 selected sites represent 5.7 percent of all the clinical study sites that enrolled subjects. The 4 sites enrolled a total of 426 subjects combined and the number of subjects enrolled at the 4 sites inspected represents 12.6 percent of subjects enrolled in the study.

Bioresearch monitoring inspections are conducted in accordance with the FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignments included specific questions related to the study protocol, and verification of the study data on efficacy endpoints submitted by the sponsor in the BLA.

PROTOCOL AUDITED

A Controlled, Multi-Center, Randomized, Open Label Phase III Study Designed to Compare the Safety and Immunogenicity of DTaP-IPV to DAPTACEL® + IPOL® as the 5th Dose Booster in Children 4 to 6 Years of Age Who Have Been Previously Vaccinated with DAPTACEL and/or Pentacel Vaccines. M5I02 Version 6.0

The table below summarizes the inspection results:

Site Number	Study Site	Location	Enrolled Subjects	483 Issued	Classification
03	Pediatrics and Adolescent Medicine, P.A.	Marietta, Georgia	39	No	NAI
04	Pediatrics and Adolescent Medicine, P.A.	Woodstock, Georgia	20	No	NAI
10	Cyn3rgy	Gresham, Oregon	20	Yes	NAI
39	Utah Valley Pediatrics, Timpanogos Office	Orem, Utah	347	Yes	VAI

NAI = No Action Indicated

FINANCIAL DISCLOSURE

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when s/he disclosed information about her/his financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children including if and when the information was updated. Each inspected study site had a copy of the financial disclosure forms on hand for the clinical investigators and sub-investigators.

INSPECTIONAL FINDINGS

Sponsor/Monitor Issues

There were no sponsor/monitor issued identified at any of the study sites audited.

Clinical Investigator (CI) Study Site Issues

A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. In addition, source documents, including records of adverse events, protocol deviations, and subject dispositions were reviewed and the information contained was compared to the data tables submitted by the sponsor in the application. Individual site observations are listed below:

Study Site 03: A Form FDA 483 was not issued at close of this inspection and the inspection was classified as NAI.

Study Site 04: A Form FDA 483 was not issued at close of this inspection and the inspection was classified as NAI.

Study Site 10: A Form FDA 483 was issued at close of this inspection. A review of the EIR revealed no significant issues impacting the study conduct and/or the data submitted by the sponsor in support of the application. The inspection received a final classification of NAI.

Study Site 39: A Form FDA 483 was issued at close of this inspection, and the inspection received a final classification of VAI. A review of the EIR revealed the following deviations from protocol:

- 138 of the 347 subjects enrolled were ineligible to participate in the study because they did not meet inclusion criteria #4, which required each subject to complete their primary infant series and boosters with DAPTACEL and/or PENTACEL vaccines before enrollment.
- 17 study subjects were administered an Investigational Product (IP) later rendered unusable by the sponsor. The sponsor deemed the IP unusable as a result of a temperature excursion experienced by the IP storage device on 2 separate occasions. The temperature excursions occurred prior to the subjects being administered the product but was not discovered until after the 17 subjects were already vaccinated with the product.

It is important to note that both these deviations were appropriately recorded and reported to the sponsor and the IRB. The FDA investigator made a comparison between the related information submitted by the sponsor in the BLA and the information reviewed at the study site, and found no discrepancy.

BIMO ADMINISTRATIVE FOLLOW-UP

Information letters were issued for all study sites inspected. Please contact me should you have any questions about this memo or any aspect of Bioresearch Monitoring.

Dennis T. Cato
Consumer Safety Officer

CC:

Access/Chron
STN 125525/0

Draft: Cato: 2/18/2015
Reviewed: Holobaugh: