DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

Memorandum

Date: April 13, 2015

From: Leslie Wagner, Chemist, LRSP/DBPAP
                Serologic Assay Reviewer

To: BLA 125563/0

                (b) (4)   (PR5I) - Diphtheria and Tetanus Toxoids and Acellular
                Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus B
                Conjugate [Meningococcal Protein Conjugate] and Hepatitis B
                [Recombinant] Vaccine

Through: Mike Schmitt, Lab Chief, LRSP/ DBPAP

Subject: Bioassay Review and Approval Memorandum
                Diphtheria & Tetanus Assay

Sponsor: MCM Vaccine Company (Sanofi Pasteur/Merck)

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General Information:
Sanofi Pasteur submitted a Biologics License Application (BLA) for "Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (DTaP-IPV-Hib- HepB)," referred to as PR5I. The proposed trade name of this product is (b) (4)   The clinical development of this vaccine in the United States was performed under BB-IND 14496, initially submitted 20 September 2010.

PR5I is a sterile fully liquid preservative-free suspension presented as a single dose in a vial for intramuscular injection. This hexavalent combination vaccine is being co-developed by Sanofi Pasteur and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. [Merck]. PR5I is manufactured using modified and/or existing bulk intermediates from vaccines licensed in the U.S. by Sanofi Pasteur and Merck.

The target indication for PR5I is for active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by Haemophilus influenzae type b and infection caused by all known subtypes of hepatitis B virus in infants at 2, 4, and 6 months of age.

This memo covers my review of the validation reports and additional data to support the use of the assays to quantitate antibodies against tetanus and diphtheria toxoids to generate pivotal data. In addition, review of the data generated in the Phase 3 studies and the repeat analysis of samples (biological validation) is provided.

Review Identifiers and Dates

Biologics License Application (BLA) Submission Tracking Number (STN): 125563/0

Submission received by CBER: August 12, 2014

Review completed: April 10, 2015

Material Reviewed:

The following general module sections of the BLA were reviewed:
- m1   Regional
- m2   Common Technical Document Summaries
- m5   Clinical Study Reports

A more detailed list of information in the BLA reviewed is provided below by amendment number:

Original submission – August 12, 2014
- m1.6   Meetings
- m2.5   Clinical Overview

- m2.7.1   Summary of Biopharmaceutical Studies and Associated Analytical Methods
- m2.7.3   Summary of Clinical Efficacy
- m5.3.1.4   Reports of Bioanalytical and Analytical Methods for Human Studies (Biological Validation)
- m5.3.5.1   Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, Studies V419-005 & V419-006

Amendment 0.6 - dated 09 April 2015
- m1.11.3   Efficacy information amendment

Related Master File, INDs and BLAs: BB-IND 14668 & BB-IND 14996

Executive Summary
This memo covers my review of the documents supporting the performance of the ELISA to quantitate antibody against the tetanus antigen, and the (b) (4) to quantitate antibody against the diphtheria antigen. This memo also addresses my review of the serologic data for tetanus and diphtheria submitted in the two Phase 3 studies (V419-005 & V419-006) designed to provide the pivotal comparative data to support the efficacy of the tetanus and diphtheria antigens in (b) (4)   (or PR5I). Protocol 005 was designed to compare the safety and immunogenicity of PR5I with licensed component vaccine controls (PENTACEL & RECOMBIVAX HB) and served as a pivotal immunogenicity study for product licensure. Protocol 006 was designed to evaluate the clinical consistency of 3 manufactured lots of PR5I. Non inferiority comparisons of PR5I immunogenicity with licensed component vaccine controls were included as secondary endpoints. In Protocols 005 and 006, the concomitant administration of PR5I with other routine licensed pediatric vaccines (i.e., RotaTeq™ and Prevnar™ (13-valent)) was also evaluated.

The validation reports and other additional data submitted in the BLA and cross referenced INDs were sufficient to support the adequate performance of the assays. No aberrant or unusual data were noted in the clinical study reports that would indicate performance issues with the assays.

Review

Serologic Assay for the Tetanus Antigen
Validation reports, SOPs and assay stability reports were cross referenced from IND 14668 in support of the data generated by these assays in the Phase 3 studies.

The following documents were submitted in support of the performance of the assays to quantitate responses to the tetanus antigen:

- Q_0277546, Method Instruction, "ELISA Method For The Determination Of Tetanus Antibodies In International Units
- Q_0249865, Validation Report for J000051, "ELISA Method for the Determination of Tetanus Antibodies in International Units"

- RED_00073544, Demonstration of the Long-Term Performance of the Anti-Tetanus (b) (4) ELISA using Plots of Control Results
- RED_00069240, Biological Validation: PR505A (Tetanus ELISA, Diphtheria (b) (4) ,Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00078360, Biological Validation: PR505B (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00077338, Biological Validation: PR506A (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00078787, Biological Validation: PR506B (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- Transfer Report for B000806 Transfer of SOP #A001837 "Determination of Diphtheria Antitoxin in International Units" from Clinical Serology Bldg. (b) (to Clinical Serology Bldg. (b) (4)
- Transfer of SWI J000051 "ELISA Method for the Determination of Tetanus Antibodies in International Units" from Bldg. (b) (to Bldg. (b) (4)
- Transfer Validation Report for SWI J000051 "ELISA Method for the Determination of Tetanus Antibodies in International Units" from Bldg. (b) (to Bldg. (b) (4)

The Tetanus (b) (4) ELISA performed by Global Clinical Immunology (GCI), Swiftwater, PA was used to quantitate the amount of anti-tetanus antibodies in human serum.

The assay used to measure anti-tetanus antibodies in human serum is based on standard direct ELISA methodology. Briefly tetanus toxin is adsorbed to plastic microtiter plates. Dilutions of samples are added and the amount of anti-tetanus antibody bound to toxin is determined by reaction with a secondary enzyme conjugated antibody, specific for (b) (4) Reaction with a substrate yields a colored product that is measured spectrophotometrically. Titers are calculated by comparison to a reference standard with assigned unitage using a (b) (4) Analysis method.

The tetanus ELISA was originally validated in 2001 and was updated in 2003 (v. 02) to re-establish the Lower Limit of Quantitation (LLOQ) from (b) (4) by including a larger number of lower concentration samples. The sponsor submitted the control trending results from November 2001 to April 2014 which included the time period in which samples from Study 005 & 006 were tested. The sponsor has maintained the same reference standard (b) (4) for this assay since 2001, however different lots of coating antigen and control sera have been used over the years. No trends were noted in the report or control charts.

The tetanus assay was originally validated in Building (b) ((Validation Report C000149) and included the following parameters: precision, accuracy, dilutability, limit of detection, and limit of quantitation. To ensure the validity of the transfer from Building (b) (to Building (b) (4) the current validation report assessed the accuracy and precision using SWI J000051 (same as Q_0277546) and documented in Transfer Report for C000586,"ELISA Method for the Determination of Tetanus Antibodies in international Units" from Bldg (b) (to Bldg (b) (4) The report states that upon review of the original

Transfer Report (C000586) in 2004, (b) (4)

Summary
The data support adequate performance parameters for the use of the tetanus assay to generate data for clinical studies with threshold and geometric mean endpoints. No issues with the validation reports were noted during review of this assay for IND 14668.

<u>Serologic Assay for the Diphtheria Antigen</u>
Validation reports, SOPs and assay stability reports were cross referenced from IND 14668 in support of the data generated by these assays in the Phase 3 studies.

The following documents were submitted in support of the performance of the assays to quantitate responses to the diphtheria antigen:

- Q_0277558, Method Instruction, "Determination of Diphtheria Antitoxin in International Units"
- Q_0293450, Validation Report for SOP #37S2, (b) (4) for Diphtheria Antitoxin"
- RED 00073616, Control Performance of Diphtheria (b) (4) from (b) (4)

- RED_00075495, Biological Validation: PR505A (Tetanus ELISA, Diphtheria (b) (4), Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00078360, Biological Validation: PR505B (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00077338, Biological Validation: PR506A (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00078787, Biological Validation: PR506B (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- Transfer Protocol B000806 "Transfer of SOP #A001837 (37S31) Determination of Diphtheria Antitoxin in International Units from Clinical Serology Bldg. (b) (to Clinical Serology Bldg. (b) (4)

- Transfer Report for B000806 Transfer of SOP #A001837 "Determination of Diphtheria Antitoxin in International Units" from Clinical Serology Bldg. (b) (to Clinical Serology Bldg. (b) (4)

The protocol states that a (b) (4) performed at Global Clinical Immunology, Swiftwater, PA was used to quantitate the amount of diphtheria toxin neutralizing antibodies in human sera.

The Sanofi serologic assay for antibodies to diphtheria is based on an assay developed in (b) (4) In general, responses to diphtheria are robust and well above the conventionally accepted sero-protective level of 0.1 IU/ml and the disease has been well controlled. Based on the general use of the assay and the reliability of the reagents, the assay appears to be robust and reliable. While the current methods and validations at Sanofi do not fully conform to currently accepted best practices, sufficient evidence was provided by the sponsor to demonstrate the assay performs adequately and is suitable for the intended purpose. We have no reason to believe that the data generated by the assay to date are unreliable, in fact the standard and control data submitted to date indicate consistent and reliable performance. Sanofi was made aware of the lack of information related to the assay and will be given the opportunity to address the weaknesses in the assay documentation for future studies.

(b) (4)

The assay was originally validated in B4 (Validation Report V04-433A, Validation Report for SOP #37S2, "(b) (4) for Diphtheria Antitoxin") and included the following parameters: precision, limit of detection, selectivity, and ruggedness. The assay was subsequently transferred between laboratories at GCI from Building (b) (to Building (b) (4) To verify the validity of the transferred assay prior to evaluation of clinical samples, precision, accuracy, specificity, and dilutability were tested, and the results showed that diphtheria (b) (4) results obtained in Building (b) (4) are equivalent to results produced in Building (b) ((Transfer Report, C000552, Transfer Report

for B000806, "Transfer of SOP #A001837, "Determination of Diphtheria Antitoxin in International Units" from Clinical Serology Bldg (b) (to Clinical Serology Bldg (b) (4) The transfer validation study (b) (4)

; the primary study endpoint for anti-diphtheria titers is based on demonstration of non-inferiority of response rates above a threshold (≥0.1 IU/mL). A Reverse Cumulative Distribution plot of the anti-diphtheria responses show that greater than 80% of subjects had titers greater than 0.1 IU/mL post 3rd dose and 100% were at least 0.6 IU/mL after the 4th toddler dose.

The diphtheria (b) (4) assay was validated in (b) (4) The sponsor submitted the control trending results from (b) (4)   , which covers the time period from validation through testing of samples for Studies 005 & 006. Different lots of critical reagents (reference, toxin, and control) have been used in this assay over time; minor trends were observed due to lot changes of reagents, however all results were within acceptable performance ranges. The Minimum Detectable Antitoxin (MDA) is defined as the lowest concentration of the reference standard that neutralizes a standard diphtheria toxin challenge dose; overall the reference has performed within the range of (b) (4)
               from (b) (4)   .

Clinical Use of the Assays
The primary immunogenicity endpoints for diphtheria and tetanus antibody response were based on geometric mean titer (GMT). In study 005, the GMT was used in the calculation of a response rate (primary endpoint); with a responder being defined as having an antibody titer ≥0.1 IU/mL. In study 006, lot consistency was evaluated by comparison of GMT ratios (primary endpoint) between treatment groups.

GMT:
This immunogenicity endpoint is based on the fact that antibody titers less than LLOQ or greater than the ULOQ were assigned a non-zero number for the purposes of calculating endpoints:

- Antibody concentrations less than the Lower Limit of Quantification (LLOQ) were assigned a value of ½ LLOQ

- Antibody concentrations greater than the Upper Limit of Quantification (ULOQ) were assigned a value of the ULOQ

Use of the definitions above requires demonstration the assay accuracy is sufficiently high and variability is sufficiently low such that values at and between the assays limits of quantitation can be measured reliably. I have reviewed the assay validation data provided by Sanofi and cross-referenced by the sponsor in IND14668 and have concluded that the sponsor has provided adequate evidence to support the above definitions.

Response Rate:
This immunogenicity endpoint is based on the proportion of subjects achieving a sero protected response, defined as having a titer ≥0.1 IU/mL post-dose 3.

Use of the antibody response definition to tetanus and diphtheria antigens requires a demonstration that the accuracy is sufficiently high and variability is sufficiently low such that values at or above 0.1 IU/mL can be reliably measured. I have reviewed the assay validation data provided by the sponsor, and have concluded that the sponsor has provided evidence to support the response definition above.

CLINICAL STUDY REPORT V419-005
A Phase III Randomized, Open-label, Active-comparator Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V419 in Infants When Given at 2, 4, and 6 Months Concomitantly With PREVNAR 13™ and ROTATEQ™

- The PR5I group received PR5I, Prevnar 13, and RotaTeq at 2, 4, and 6 months followed by DAPTACEL, PedvaxHIB and Prevnar 13 at 15 months

- The Control group received PENTACEL, Prevnar 13, and RotaTeq at 2, 4, and 6 months and Recombivax HB at 2 and 6 months followed by DAPTACEL, ActHIB and Prevnar 13 at 15 months

Primary Objectives (Immunogenicity)
1. To compare the immunogenicity of PR5I with the component vaccine Control(s).
2. To compare the immunogenicity of pertussis responses at one month after the Toddler dose of DAPTACEL after receiving an infant series of either 3 doses of PR5I or PENTACEL.
3. To demonstrate that the inactivated poliovirus (IPV) response rate is acceptable after receiving an infant series of 3 doses of PR5I.

Primary Immunogenicity Endpoint (Diphtheria & Tetanus)
Primary immunogenicity endpoint for the evaluation of non-inferiority to the licensed component vaccine control included the response rates for all licensed component vaccine control antigens included in PR5I at one month after the third dose (Postdose 3).

Tertiary Objectives (Diphtheria & tetanus immunogenicity)
1. To describe the GMTs for all antigens in PR5I and the component vaccine control(s) at Postdose 3 with 95% CI.
2. To describe the response rates to all antigens (i.e., diphtheria, tetanus, and Hib), except pertussis one month after the Toddler Dose with 95% CI.

Diphtheria
The results of the response rates for the diphtheria antigen one month post-dose 3 (infant series) indicate that subjects in both vaccination groups had similar response rates against the diphtheria antigen with >80% subjects achieving a sero-protected

antibody level of ≥0.1 IU/mL. Post-dose 4 (toddler booster), the percentage of subjects achieving a sero-protective antibody level was 100% for both groups.

Tetanus
One month post-dose 3 (infant series) the subjects in both vaccination groups achieved similar response rates (> 99% subjects ≥0.1 IU/mL) against the tetanus antigen. After the Toddler dose, the percentage of subjects achieving a sero-protective antibody level was 100% for both groups.

The reverse cumulative distribution curves of the antibodies to tetanus and diphtheria antigens showed that the curves for the subjects who received PR5I were the same shape as the curves for the subjects who received Control vaccines indicating that the response is consistent between groups. Review of all data, show no aberrant results.

CLINICAL STUDY REPORT V419-006
A Phase III Randomized, Partially Double-Blind, Active-Comparator Controlled, Lot-to-Lot Consistency Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V419 in Healthy Infants When Given at 2, 4, and 6 Months Concomitantly With PREVNAR 13™ and ROTATEQ™

- The PR5I group received PR5I, Prevnar 13™ and RotaTeq™ at 2, 4, and 6 months followed by PENTACEL™ and Prevnar 13™ at 15 months

- The Control group received PENTACEL™, Prevnar 13™, and RotaTeq™ at 2, 4, and 6 months, RECOMBIVAX HB™ at 2 and 6 months, and PENTACEL™ and Prevnar 13™ at 15 months

Primary Objective (Immunogenicity)

To evaluate the consistency of the Post-dose 3 immune response to 3 manufactured lots of PR5I when given at 2, 4, and 6 months of age with respect to geometric mean titers (GMTs).

Primary & Secondary Immunogenicity Endpoints (Diphtheria & Tetanus)

- The primary endpoint for the primary hypothesis of lot consistency was the GMTs for all antigens contained in PR5I one month after the third dose of PR5I.

- Secondary immunogenicity endpoint for the evaluation of non-inferiority to the licensed component vaccine control included the response rates for all licensed component vaccine control antigens included in PR5I at one month after the third dose (Post-dose 3).

Secondary Objectives (Immunogenicity)
1. To evaluate the consistency of the Post-dose 3 immune response to 3 manufactured lots of PR5I when given at 2, 4, and 6 months of age with respect to response rates.
2. To compare the immunogenicity of pertussis responses at one month after the Toddler dose of PENTACEL™ after receiving an infant series of either 3 doses of PR5I or PENTACEL™.
3. To compare the immunogenicity of PR5I with the component vaccine Control at one month after the third dose.
4. To evaluate the immunogenicity of Prevnar 13™ (at Post-dose 3) when administered concomitantly with PR5I.

Tertiary Objectives (Immunogenicity)
1. To describe the response rates and GMTs to all antigens in PR5I and the component vaccine Control at one month Post-dose 3 with 95% confidence interval (CI).
2. To describe the response rates and GMTs to all antigens one month after the Toddler dose with 95% CI.

Diphtheria & Tetanus
RCD curves of the GMT for the per protocol population with the revised window show that for both anti-tetanus and anti-diphtheria titers, one month post-dose 3, the lines representing the 3 lots were close to each other at each time point, indicating comparable responses.

Anti-diphtheria responses post-dose 3 were generally robust, with at least 85% of subjects in all groups achieving response ≥ 0.1 IU/mL. The point estimate for all groups after the infant series was >0.3 IU/mL and this increased approximately 10-fold with the subsequent toddler dose (4th dose).

Greater than 99% of subjects in all groups have achieved sero-protective (≥ 0.1 IU/mL) anti-tetanus antibody levels post dose 3. The tetanus antibody response was greater for the PR5I groups as compared to Control, however all groups achieved a sero-protected level. This is reflected in the RCD curves for the Control group shifted left (lower) as compared to the PR5I group. The higher point estimate in study 006 and non-overlapping 95% CI of GMT was also observed in study 005.

Re-testing
To confirm that the assays used to generate the data used in the study were performing adequately and that no data were inappropriately excluded from the analysis, the sponsor submitted the Biological Validation Reports for studies 005 & 006.

Biological validation (BV) is a study-level verification process, defined within Q_0234877, Biological Validation of Clinical Testing Results within Global Clinical Immunology, Sanofi Pasteur, Swiftwater that is applied to the overall population of study results generated by the testing of clinical samples. The BV process is considered to be a

quality measure applied to each test method at the completion of testing and is independent from internal quality criteria applied to individual samples and test runs. Suspect results are identified and the BV process provides a method by which identified results can be verified prior to the final data set being released. The sponsor submitted to the BLA four reports detailing the statistical analysis, retest results, and replacement of data points in studies 005 & 006.

Biological Validation Reports:
- RED_00075495, Biological Validation: PR505A (Tetanus ELISA, Diphtheria (b) (4),Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00078360, Biological Validation: PR505B (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00077338, Biological Validation: PR506A (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))
- RED_00078787, Biological (b) (4) PR506B (Tetanus ELISA, Diphtheria (b) (4) Polio (b) (4) and Pertussis US (b) (4) (PRN, FHA, FIM, PT))

Review of the data indicated that the sample retesting and replacement was evenly distributed between the study groups and unlikely to cause bias. In addition a very small number of values were replaced due to retesting. Review of all testing data did not find any aberrant or unusual data that would indicate issues with assay performance.

Assay stability over time was confirmed in an Information Request (3/17/15) sent to the sponsor. The sponsor stated in their response (4/9/15) that the assay stability information had been previously submitted to IND 14668 (Quadracel) on 7/31/14 in Serial 021.

- RED_00073616, *Control Performance of Diphtheria* (b) (4) *from* (b) (4)

- RED_00073544, *Demonstration of the Long-Term Performance of the Anti-Tetanus* (b) (4) *ELISA using Plots of Control Results*

The sponsor provided the dates samples were tested from study 005 (7/17/12 – 9/5/13) and study 006 (12/3/12 – 11/27/13). Plots of the reference and internal positive controls were presented from validation through testing of samples for studies 005 & 006. The graphs included information when lot changes occurred for key reagents. No trends were noted.

Recommendation
The immunoassays used to measure the antibody response to the diphtheria and tetanus components of PR5I are adequate for the purposes for which they were used in this application. Demonstration of acceptable performance of the assays is essential in order to approve this Biologics License Application (BLA) because immunogenicity data provide the primary evidence supporting comparability of the new combination vaccine to the currently licensed.

On August 12, 2014 MVM submitted an original BLA with Clinical Efficacy Data to support a label claim. I have reviewed all documents relating to immunoassay performance of the diphtheria and tetanus assays for SPL supplement STN 125563/0; the clinical data, assay validation reports and data supporting assay performance since validation indicate the assays were performing as expected. Serologic data in support of studies 005 & 006 appear to have been generated in assays adequate for that use.

I recommend approval of the application.