



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration Silver Spring MD 20993

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 Center for Biologics Evaluation and Research (CBER)
 Food and Drug Administration (FDA)

TO: Biologics License Application Submission Tracking Number # 125563/0

SUBJECT: Clinical Serology and Bioassay Review, and Approval Memorandum

PRODUCT: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus B Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine

THROUGH: Jay Slater, M.D., Director
 Division of Bacterial, Parasitic and Allergenic Products

APPLICANT: MCM Vaccine Company (Sanofi Pasteur/Merck)

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1. 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 (Hib) 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 Hib to generate pivotal data. In addition, review of the data generated in the Phase 3 studies is provided.

1.1. Review Identifiers and Dates

1.1.1. Biologics License Application Submission Tracking Number (STN) #

125563/0

1.1.2. Submission received by CBER

13 August 2014

1.1.3. Review completed

2 March 2, 2015

1.1.4. 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 dated 13 August 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
m5.3.5.1 Study Reports of Controlled Clinical Pertinent to the Claimed Indication, v419-005, v419-006
m5.3.5.3 Reports of Analyses of Data from More than One Study Integrated Summary of Efficacy

1.1.5 Related Master File, INDs and BLAs

BB-IND 4011

2. Summary

The (b) (4)) used to quantitate antibodies against Hib was originally validated by Merck in 1997 and transferred to the Wayne, PA facility in 2002. In 2008, Merck sold the Wayne facility and the Hib anti-PRP (b) (4), Inc., thus the assay location has remained unchanged since 2002. The samples from the PR5I Phase III United States studies were tested in the Hib anti-PRP (b) (4) from December 2011 through November 2013.

This BLA, 125563/0, cross referenced IND 4011 for the validation, assay transfer and assay stability data. Comments regarding the long term use of the Hib assay, validated in 1997, have been sent to (b) (4) under MF (b) (4). Outstanding issues are not considered to affect the interpretation of the data generated by that assay in support of licensure of the PR5I vaccine. In addition, assay stability data submitted to IND 4011 (control and reference data through 2013) and continued control of Hib disease in this country indicate no major issues with the assay. The assay is likely adequate for use to support the studies under this IND.

The clinical data generated using the Hib (b) (4) have been reviewed and no aberrant results were identified that would indicate assay performance issues. The clinical data support the noninferiority of the Hib antigen in PR5I when compared to the control groups, and the consistency of the immunogenicity of three lots of vaccine in studies 005 and 006.

3. Review

A BLA/BB-IND reference authorization letter dated 8-July-14 from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., gave authorization to the Food and Drug Administration to review information contained in STN 103237 and BB-IND 4011 as part of the review of the BLA for PR5I.

3.1. Serologic Assays for Hib antigen

The SOPs, and validation and assay stability reports below were specifically cross referenced to support performance of the Hib (b) (4) under BLA 125563/0.

Table 1. Documentation provided in support of the PRP (b) (4)

Documentation	IND / Serial / Module	Date
Validation Documentation	BB-IND 4011, Serial 0135, mod. 1.11.3	02-Jun-2014
SOP for Assay	BB-IND 4011, Serial 0135, mod. 1.11.3	02-Jun-2014
Data Stability of Assay	BB-IND 4011, Serial 0135, mod. 1.11.1	14-Jan-2014

The following documents were submitted and reviewed:

Statistical Report: Validation of the Anti-PRP Antibody Assay, revised 28 April 1997

Parallel Testing to Transfer the anti-PRP, *Haemophilus influenzae* Type b (HIB) (b) (4) (SOP #910.0025) from CAR&D MRL-West Point to CAR&D MRL-Wayne, 11 April 2002

SOP VBL.3629_3.2, *Haemophilus influenzae* type b (b) (4)

Response to CBER Question 1 from 16 October 2013 Information Request regarding assay stability data for the Hib (b) (4) IND 4011 amendment 133, submitted 14 January 2014, Section 1.11.1, Quality Information Amendment

The Hib (b) (4) detects antibody specific to *Haemophilus influenzae* type b capsular polysaccharide (polyribosylribitol phosphate, PRP) in human sera. In the (b) (4)

The human anti-*Haemophilus influenzae* type b capsular polysaccharide antibody Lot (b) (4) was provided by the Center for Biologics Evaluation and Research (CBER) and has a concentration of (b) (4). Three individual human sera developed at (b) (4) were used as controls for the (b) (4)

The validation report contains data with regard to precision, dilution recovery (linearity), limit of detection (LOD), and lower limit of quantitation (LLOQ) of the (b) (4) assay.

Precision: In order to demonstrate precision, (b) (4)

Limit of detection: The LOD was determined (b) (4)

Limit of quantitation: The limit of quantitation was defined as (b) (4)

Dilution effect (Linearity): Dilution effect was determined using (b) (4)

While the extent of the data and the validation analyses were consistent with validation practices when validated in 1997. The validation data support the precision of the assay (b) (4)

When the assay was transferred to the Wayne laboratory from West Point, a comparability study between the laboratories was performed by testing (b) (4)

However, overall the data suggest that the assay as run at Wayne is not substantively different than that run at West Point.

(b) (4)

3.2. Clinical Study Data for the *Haemophilus influenzae* Type B Antigen (PRP)

The two clinical studies used to generate the primary data for immunogenicity for the Hib antigen are included in this review (005 and 006).

Protocol No: 005-04: 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

This study was a randomized, active comparator-controlled, open-label, multicenter study in healthy infants (46 to 89 days of age at enrollment) to assess the safety, tolerability, and immunogenicity of PR5I when administered concomitantly with the licensed vaccines Prevnar 13 and RotaTeq.

A total of 1473 healthy infants, who had received a dose of monovalent hepatitis B vaccine outside of the study context as part of standard medical practice at birth prior or up to approximately one month of age, were randomized in a 2:1 ratio to receive either PR5I or the component vaccine Control(s). The subjects randomized to 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 subjects randomized to the Control group received the same vaccine regimen as the PR5I group with respect to concomitant vaccines, but the Control group received PENTACEL at 2, 4, and 6 months and Recombivax HB at 2 and 6 months followed by DAPTACEL, Prevnar 13 and ActHIB at 15 months. Prevnar 13 was supplied by the investigator or by the site as needed. The Hib conjugate vaccine administered at 15 months for the PR5I and Control groups were chosen to preserve antigenic continuity throughout the Hib vaccination series.

Primary Objectives relevant to Hib responses:

1. To compare the immunogenicity of PR5I with the component vaccine Control(s).

The statistical criteria for non-inferior antibody response to PRP required that:

- a. the lower bound of the 2-sided 95% Confidence Interval (CI) for the difference in percent of subjects with anti-PRP ≥ 1.0 $\mu\text{g/mL}$ (PR5I group minus Control group) is greater than -10%, and
- b. the lower bound of the 2-sided 95% CI for the difference in percent of subjects with anti-PRP ≥ 0.15 $\mu\text{g/mL}$ (PR5I group minus Control group) is greater than -5%.

The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP $\geq 0.15 \mu\text{g/mL}$ one month Postdose 3 was 4.87% (95% CI: 2.23% to 8.14%); the lower bound of the 2-sided 95% CI for the difference was $>5\%$. The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP $\geq 1.0 \mu\text{g/mL}$ one month Postdose 3 was 9.68% (95% CI: 4.83% to 14.83%); the lower bound was $> -10\%$. Thus, non-inferiority was demonstrated.

Secondary Objectives relevant to the Hib antigen (PRP):

1. To compare anti-polyribosylribitol phosphate (PRP) responses elicited by PR5I with the component vaccine Control(s).

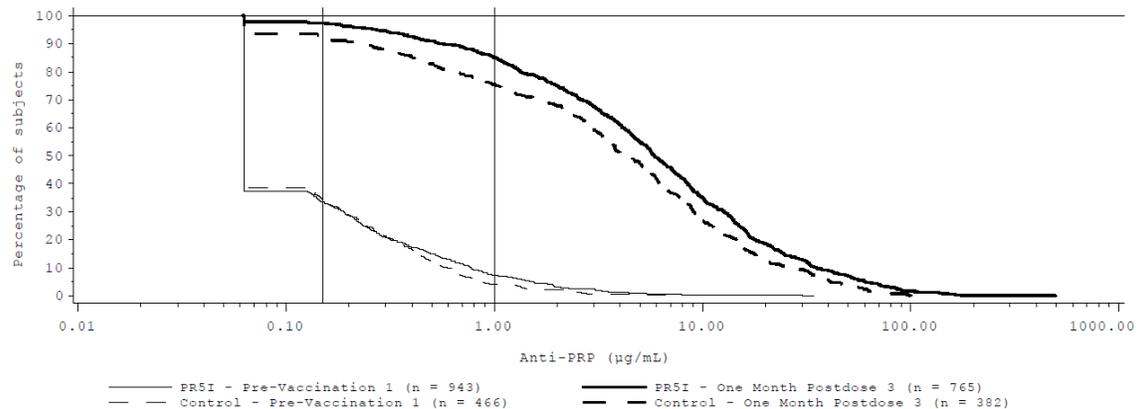
The statistical criteria for non-inferior antibody response to PRP require that:

- a. the lower bound of the 2-sided 95% CI for the difference in percent of subjects with anti-PRP $\geq 0.15 \mu\text{g/mL}$ (PR5I group minus Control group) is $> -10\%$, and
- b. the lower bound of the 2-sided 95% CI of the GMT ratio (PR5I group/Control group) is > 0.67 .

The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP $\geq 0.15 \mu\text{g/mL}$ at one month Postdose 3 was 4.87% (95% CI: 2.23% to 8.14%; $p\text{-value} < 0.001$); indicating a non-inferior antibody response in the PR5I group compared to the Control group (97.26% vs. 92.39%).

The GMT ratio (PR5I group/Control group) one month Postdose 3 was 1.62 (95% CI: 1.32 to 1.98; $p\text{-value} < 0.001$); the lower bound of the 2-sided 95% CI for the ratio was >0.67 also indicating a non-inferior response in the PR5I group compared to the Control group (4.94 vs. 3.05).

Figure 1. Reverse cumulative distribution curves pre and post dose 3 for PRP



The reverse cumulative distribution curves are consistent with the analytical results.

Review of the data did not find any aberrant or unusual data that would indicate issues with assay performance.

Protocol No.: 006-02A 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.

This was a randomized, partially double-blind, active comparator-controlled, multicenter, lot-to-lot consistency study in healthy infants (46 to 89 days of age at enrollment) to (1) provide data regarding the ability of PR5I to induce a consistent immune response, (2) assess the immune responses elicited by the concomitant administration of PR5I and Prevnar 13, and (3) describe the safety profile of PR5I and the component comparator Control.

A total of 2808 healthy infants, who had received a dose of monovalent hepatitis B vaccine outside of the study context, as part of standard medical practice, were randomized into one of 4 vaccination groups (ratio 2:2:2:1). The subjects randomized to the PR5I groups (3 different lots to measure lot consistency, approximately 800 subjects per group) received PR5I, Prevnar 13 and RotaTeq at 2, 4, and 6 months followed by PENTACEL and Prevnar 13 at 15 months. The subjects randomized to the Control group (402 subjects) 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. Subjects and study personnel were blinded to which of the 3 PR5I lots were administered to a given subject, but aware of assignment to PR5I vs. Control.

Primary Objective relevant to Hib responses:

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 geometric mean titers (GMTs).

The statistical criteria require that, for each of the PR5I antigens, the 2-sided 95% CIs of the GMT ratios between any 2 lots are within the equivalence margin (0.67 to 1.5).

For PRP the number of subjects contributing data to the analysis for each lot ranged from 595 to 604. The point estimates for the GMT ratios ranged from 0.86 to 0.94 with the lowest lower 95% CI at 0.72 and the highest upper 95% CI at 1.12 (see table 11-1 in the clinical study report). The criteria were met.

Secondary Objectives relevant to Hib responses:

1. To evaluate the consistency of the Postdose 3 immune response to 3 manufactured lots of PR5I when given at 2, 4, and 6 months of age with respect to response rates.

The statistical criteria require that, for each of the PR5I antigens, the 2-sided 95% CIs of the response rate difference between any 2 lots are within the equivalence margin

The differences between the response rates comparing each lot ranged from -0.48 to -1.62. The highest absolute value for the 95% CI for the differences was 5.38, within the 10% absolute difference criterion.

3. To compare the immunogenicity of PR5I with the component vaccine Control at one month after the third dose.

The statistical criteria for non-inferior antibody response to PRP require that:

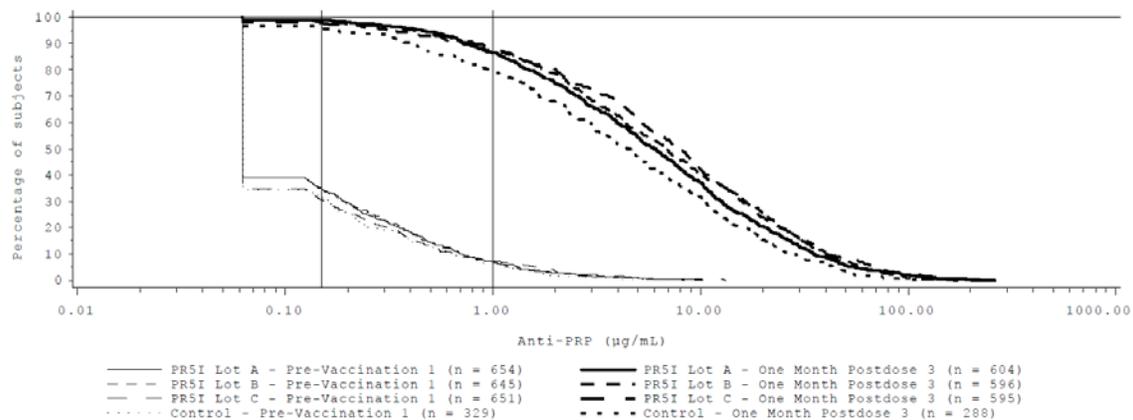
- i. the difference in percent of subjects with anti-PRP $\geq 1.0 \mu\text{g/mL}$ (PR5I group minus Control group) is greater than -10%.
- ii. the difference in percent of subjects with anti-PRP $\geq 0.15 \mu\text{g/mL}$ (PR5I group minus Control group) is greater than -5%.
- iii. the lower limit of the 2-sided 95% CI of the GMT ratios (PR5I group/Control group) is > 0.67 .

The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP $\geq 1.0 \mu\text{g/mL}$ one month Postdose 3 was 7.93% (95% CI: 3.38% to 13.17%); the lower bound was $> -10\%$. The difference (PR5I group minus Control group) regarding the proportion of subjects with anti-PRP $\geq 0.15 \mu\text{g/mL}$ one month Postdose 3 was 2.20% (95% CI: 0.39% to 5.12%); the lower bound of the 2-sided 95% CI for the difference was $> -5\%$. Thus, non-inferiority was demonstrated.

The GMT ratio (PR5I group/Control group) one month Postdose 3 was 1.63 (95% CI: 1.35 to 1.98); the lower limit of the 2-sided 95% CI was > 0.67 . Thus, non-inferiority was demonstrated.

The reverse cumulative distribution curves are consistent with the clinical analyses.

Figure 2. Reverse cumulative distribution curves for the three lots for PRP



Review of the line listings for the PRP data did not find any aberrant or unusual data that would indicate issues with assay performance.

4. Recommendation

The data supporting the performance of the serologic assay used to generate the PRP response data in Studies 005 and 006 are sufficient and indicate that the assay performs adequately for its intended use. The data from studies 005 and 006 indicate that PR5I did not induce inferior immune responses to the Hib antigen relative to the control vaccines and the responses to the Hib component were consistent among lots.

I recommend approval of this BLA.