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**DATE:** December 9, 2014

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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 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 pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM) to generate pivotal data. In addition, the data generated in the Phase 3 studies and the repeat analysis of samples (biological validation) is provided.

**1.1. Review Identifiers and Dates**

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

125563/0

1.1.2. Submission received by CBER

13 August 2014

1.1.3. Review completed

December 9, 2014

1.1.4. Material Reviewed

The following general module sections of the BLA were reviewed:

ml                      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
m5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies
m5.3.5.1	Study Reports of Controlled Clinical Pertinant 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 14496, BB-IND 14668

## 2. Executive Summary

This memo covers my review of the documents supporting the performance of the (b) (4) to quantitate antibody against the pertussis antigens (PT, FHA, PRN, FIM) in the vaccines. This memo also addresses my review of the serologic data for pertussis submitted in the two Phase 3 studies (005 and 006) designed to provide the pivotal comparative data to support the efficacy of the pertussis antigens in PR5I.

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.

The serologic data in the study reports for studies 005 and 006 were consistent and demonstrated noninferiority of the PT and FIM responses to PR5I when compared to the control groups. In both studies, however, the lower 95% confidence intervals (CI) of the ratio of the geometric mean titers (GMT) against FHA (GMT of PR5I/Control) were below the criterion of 0.67 post third dose. The reverse cumulative distribution curves for the responses to FHA were evaluated and the difference in the GMTs between the groups does not translate to a higher number of nonresponders or substantially higher number of seronegative subjects post vaccination. Responses to the other pertussis antigens were not diminished in the PR5I group relative to the control. The difference in the GMTs to FHA is unlikely to translate into a loss of efficacy of the

vaccine. The PRN data analysis in Study 006 also indicated that the lower 95% CI of the ratio of the GMT was less than 0.67 post toddler dose. Similar to FHA, the reverse cumulative distribution curves did not indicate that the difference in the GMTs between the groups translated to a higher number of nonresponders or substantially higher number of seronegative subjects post vaccination. In all cases where the criterion for the ratio of GMTs was not met, the criterion for differences between responder rate was met. The data overall indicate that reduction of immunogenicity in PR5I based on GMT is unlikely to have a substantive effect on vaccine efficacy.




### 3. Review

#### 3.1. Serologic Assays for the Pertussis Antigens

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.


Specifically, the SOPs and validation reports below were relevant to this BLA.

(b) (4)





(b) (4)



#### Summary

The data support adequate performance parameters for the use of this assay to generate data for clinical studies with threshold, fold rise and geometric mean endpoints. Minor issues with the validation reports were noted during review of these assays for IND 14668 with comments sent to the applicant and adequate responses received 15 November 2013 (amendment 15).

### 3.2. Clinical Study Data for the Pertussis Antigens

The two clinical studies used to generate the primary data for immunogenicity for the pertussis antigens are included in this review (005 and 006). Included in the BLA for each study is a separate Biological Validation Report describing the sample retesting performed during each study for the assays performed at Sanofi Pasteur. For the two studies reviewed here, retesting was based on an analysis of the initial sample data with the sample information code broken to identify the sample timepoint but not the group. Samples identified as outliers or samples where the prevaccination sample was greater than the post vaccination sample were retested. If the second test did not agree with the first, a third test was performed. If the third test did not confirm either of the first two tests, the sample value was not reported. Review of the relevant Biological Validation Reports is included for each study.

#### **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 RotaTaq 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:

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.

Immunogenicity against the pertussis antigens was assessed using both response rates and geometric mean titers (GMT) For the pertussis antigens, responses were defined as follows (1) if prevaccination antibody concentration was  $< 4 \times \text{LLOQ}$ , then the postvaccination antibody concentration should be  $\geq 4 \times \text{LLOQ}$ , (2) if prevaccination antibody concentration was  $\geq 4 \times \text{LLOQ}$ , then the postvaccination antibody concentration should be  $\geq$  prevaccination levels. The criteria for success were that the lower 95% confidence interval (CI) for response rates had to be greater than 10% and the lower 95% CI for the ratio of the GMT had to be greater than 0.67. The summary data are tabulated below for the per protocol population using the revised wider window for blood draw post 3<sup>rd</sup> dose (Table 11-1 from the report).

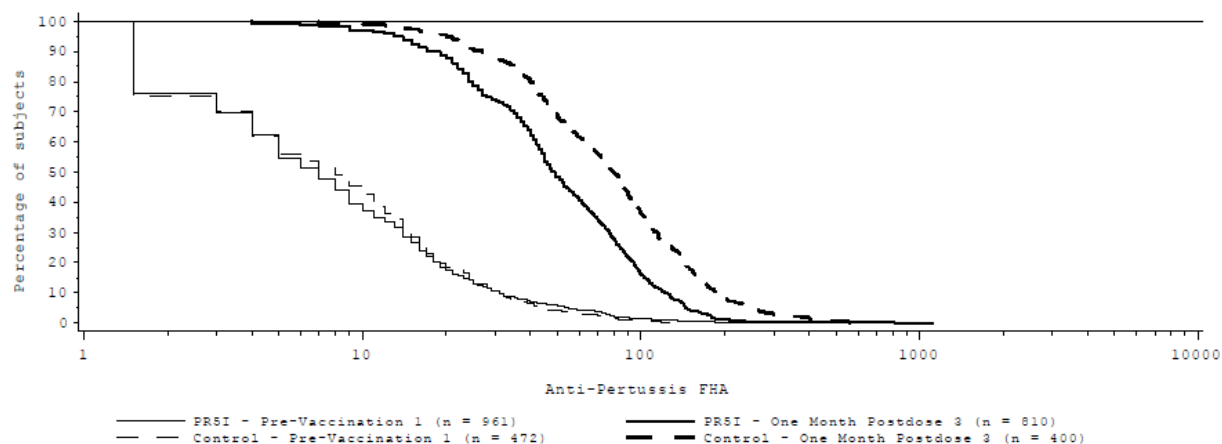
Table 1. Analysis of Non-Inferiority Regarding Pertussis Antigen Responses One Month Postdose 3

Antigen	PR5I (n=796-810)	Control (n=390-400)	Estimated difference/GMT Ratio (95% CI)
PT % response rate	98.12	98.45	-0.33 (-1.80, 1.60)
FHA % response rate	87.33	92.04	-4.70 (-8.14, -0.97)
PRN % response rate	79.34	82.01	-2.67 (-7.27, 2.23)
FIM % response rate	90.20	86.15	4.05 (0.23, 8.28)
PT GMT	109.61	85.41	1.28 (1.20, 1.38)

FHA GMT	46.59	72.28	0.64 (0.59, 0.70)
PRN GMT	55.77	66.81	0.83 (0.73, 0.95)
FIM GMT	235.87	184.40	1.28 (1.15, 1.42)

The primary endpoint for the GMT ratio for FHA was not met. Reverse cumulative distribution curves were provided for the per protocol population with the revised window. Below is the curve for FHA titers (taken from Figure 14-6 in the report).

Figure 1. Reverse Cumulative Distribution Curve for Anti-Pertussis FHA antigens by vaccination



The curve for the PR5I recipients is shifted left as expected. The curves begin to diverge between titers of approximately 10 to 20 (b) (4). The difference in the GMTs between the groups does not translate to a higher number of nonresponders or substantially higher number of seronegative subjects post vaccination. Responses to the other pertussis antigens were not diminished in the PR5I group relative to the control. The difference in the GMTs to FHA is unlikely to translate into a loss of efficacy of the vaccine.

The summary data are tabulated below for the per protocol population using the revised wider window for blood draw post toddler dose (Table 11-3 from the report).

Table 2. Analysis of Non-Inferiority Regarding Pertussis Antigen Responses One Month Toddler Dose

Antigen	PR5I (n=699-713)	Control (n=349-358)	Estimated difference/GMT Ratio (95% CI)
PT % response rate	99.28	97.40	1.88 (0.39, 4.18)
FHA % response rate	94.44	93.14	1.30

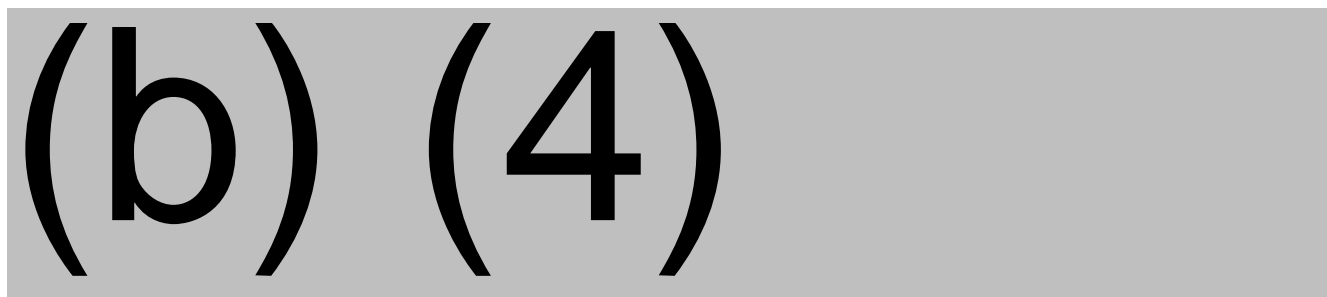


			(-1.67, 4.78)
PRN % response rate	93.00	93.41	-0.41 (-3.46, 3.10)
FIM % response rate	97.30	91.12	6.18 (3.26, 9.78)
PT GMT	126.90	90.78	1.40 (1.28, 1.52)
FHA GMT	87.52	87.54	1.00 (0.91, 1.10)
PRN GMT	108.48	139.71	0.78 (0.68, 0.89)
FIM GMT	657.28	415.00	1.58 (1.41, 1.78)

All endpoints were met for all antigens.

The Biological Validation Report listed all samples retested with results from all testing. The following table summarizes the retesting performed. Based on the statistical criteria applied, one would expect approximately 1% of the samples to be retested based on chance alone.

Table 3. Summary of retesting for Study 005



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.

**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.**

Primary Objective:

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).

Secondary Objectives relevant to pertussis 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 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.

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.

Immunogenicity against the pertussis antigens was assessed using both response rates and geometric mean titers (GMT) For the pertussis antigens responses were defined as follows (1) if prevaccination antibody concentration was  $< 4 \times \text{LLOQ}$ , then the postvaccination antibody concentration should be  $\geq 4 \times \text{LLOQ}$ , (2) if prevaccination antibody concentration was  $\geq 4 \times \text{LLOQ}$ , then the postvaccination antibody concentration should be  $\geq$  prevaccination levels. Equivalence was defined as a lower 95% confidence interval (CI) for response rates greater than 10% and a lower 95% CI for the ratio of the GMT greater than 0.67. The table below summarizes the GMT data below for the per protocol population using the revised wider window for blood draw post dose 3 (Table 11-1 from the report).

Table 4. Anti-pertussis GMTs by lot

Antigen	Lot A (n=632-644)	Lot B (n=616-634)	Lot C (n=611-628)	Lot A/Lot B	Lot A/Lot C	Lot B/LotC
PT	100.83	96.82	98.52	1.03 (0.96, 1.10)	1.02 (0.95, 1.09)	0.99 (0.92, 1.06)
FHA	43.98	49.19	56.93	0.89 (0.83, 0.96)	0.78 (0.72, 0.83)	0.87 (0.81, 0.94)
PRN	51.30	52.32	54.78	0.97	0.93	0.96

				(0.87, 1.09)	(0.83, 1.05)	(0.85, 1.08)
FIM	228.78	286.74	283.28	0.78 (0.72, 0.85)	0.80 (0.73, 0.87)	1.02 (0.93, 1.11)

The response rates against the pertussis antigens were also equivalent among the lots.

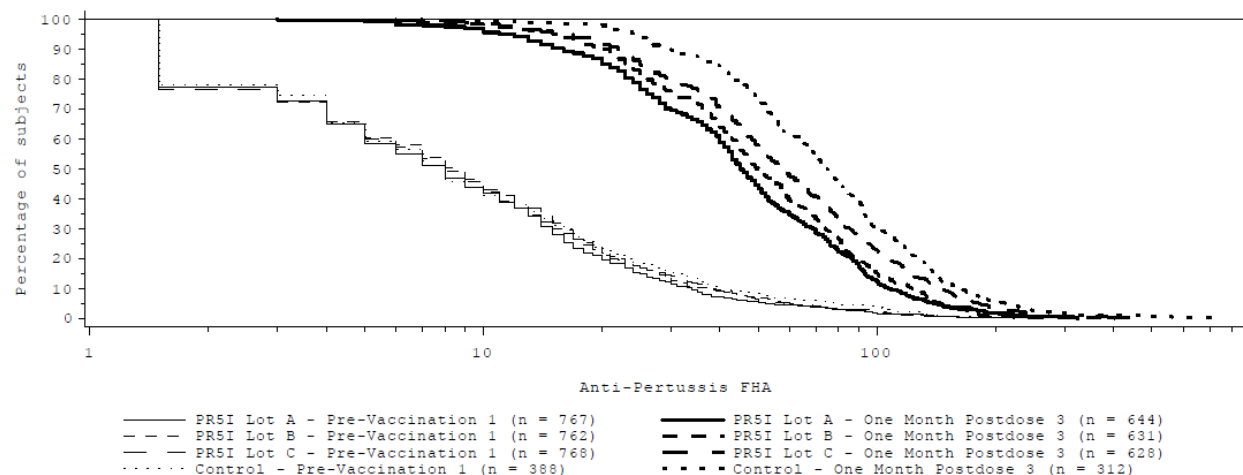
The comparison between the groups who received the PR5I vaccine and the group who received the control vaccines is presented in the table below for the per protocol revised window population (from Table 11-5 in the report).

Table 5. Analysis of Non-Inferiority Regarding PR5I Antigen Responses at One Month Post Dose 3

Antigen	PR5I (n=1724-1903)	Control (n=286-312)	Estimated difference/GMT Ratio (95% CI)
PT % response rate	98.64	97.92	0.72 (-0.59, 3.14)
FHA % response rate	87.42	92.12	-4.70 (-7.73, -0.86)
PRN % response rate	79.48	76.19	3.28 (-1.70, 8.85)
FIM % response rate	89.67	86.82	2.85 (-0.85, 7.36)
PT GMT	95.60	79.89	1.20 (1.11, 1.29)
FHA GMT	46.45	69.10	0.67 (0.62, 0.73)
PRN GMT	52.84	51.49	1.03 (0.90, 1.17)
FIM GMT	255.32	168.97	1.51 (1.37, 1.66)

The primary endpoint for the GMT ratio for FHA was not met. Reverse cumulative distribution curves were provided for the per protocol population with the revised window. Below is the curve for FHA titers (taken from Figure 14-6 in the report).

Figure 2. Reverse Cumulative Distribution Curve for Anti-Pertussis FHA antigens by Vaccination Post Dose 3



The curves for the PR5I recipients are shifted left as expected. The curves begin to diverge from the control curve between titers of approximately 10 to 20 (b) (4). The difference in the GMTs between the groups does not translate to a higher number of nonresponders or substantially higher number of seronegative subjects post vaccination. Responses to the other pertussis antigens were not diminished in the PR5I group relative to the control. The difference in the GMTs against FHA is unlikely to translate into a loss of efficacy of the vaccine.

Immunogenicity of a booster dose of PENTACEL, given to subjects in all groups, was compared between those who received PR5I and those who received control vaccines for the first three doses. The table below presents the data for the per protocol revised window population (from Table 11-9 in the report)

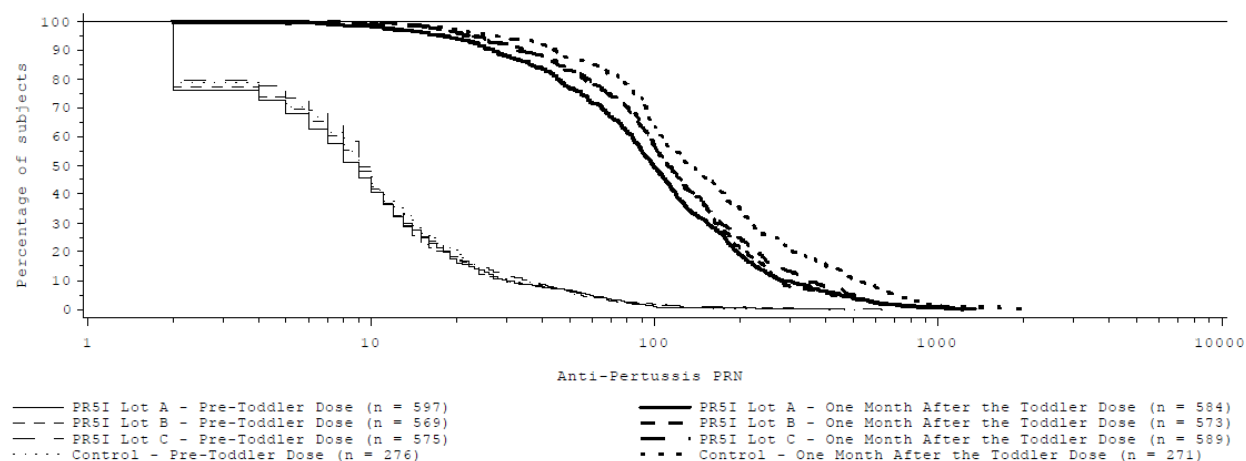
Table 5. Analysis of Non-Inferiority Regarding PR5I Antigen Responses at One Month Post Toddler Dose

Antigen	PR5I (n=1608-1746)	Control (n=254-271)	Estimated difference/GMT Ratio (95% CI)
PT % response rate	98.51	98.40	0.12 (-1.11, 2.58)
FHA % response rate	95.32	95.48	-0.16 (-2.41, 3.22)
PRN % response rate	92.18	91.03	1.15 (-2.13, 5.47)
FIM % response rate	93.00	90.00	3.00 (-0.39, 7.40)
PT GMT	104.94	98.26	1.07 (0.98, 1.17)
FHA GMT	98.98	114.65	0.86 (0.79, 0.95)
PRN GMT	105.33	141.88	0.74

			(0.66, 0.83)
FIM GMT	426.42	325.86	1.31 (1.17, 1.46)

The endpoint for the GMT against PRN did not meet the criteria. Reverse cumulative distribution curves were provided for the per protocol population with the revised window. Below is the curve for PRN titers (taken from Figure 14-8 in the report).

Figure 3. Reverse Cumulative Distribution Curve for Anti-Pertussis PRN antigens by Vaccination Post Toddler Dose



As seen with the FHA data post dose 3, the curves for the PR5I recipients are shifted left as expected. The curves begin to diverge from the control curve at approximately 30(b) (4). The difference in the GMTs between the groups does not translate to a higher number of nonresponders or substantially higher number of seronegative subjects post vaccination. Responses to the other pertussis antigens were not diminished in the PR5I group relative to the control. The difference in the GMTs to PRN is unlikely to translate into a loss of efficacy of the vaccine.

The Biological Validation Report listed all samples retested with results from all testing. The following table summarizes the retesting performed. Based on the statistical criteria applied, one would expect approximately 1% of the samples to be retested based on chance alone.

Table 3. Summary of retesting for Study 006

(b) (4)

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. However, for PRN assay, of the (b) (4) samples slated for retesting, 40 did not have sufficient quantity for full retesting. For the FHA assay, 106 of the (b) (4) samples slated for retesting did not have sufficient quantity for retesting. The data for these samples were removed from the analysis. This practice of removal of data with unexpected results due to insufficient volume for retesting could bias the data in favor of higher response rates and tighter confidence intervals. The retesting practices of the applicant should continue to be monitored to assure that it does not introduce bias in future studies.

Review of all testing 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 assays used to generate the data in Studies 005 and 006 are sufficient and indicate that the assays perform adequately for their intended use. The data from studies 005 and 006 indicate that PR5I did not induce inferior immune responses to the pertussis antigens that could be considered clinically relevant to the efficacy of the pertussis components.

I recommend approval of this BLA.