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To: File, BLA 125563

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Subject: Serology review memo of the immune response against the concomitantly administered Prevnar13® with the investigational vaccine PR51 developed jointly by Merck Sharp & Dohme Corp and Sanofi Pasteur SA. PR51 is composed of Merck vaccines, PedvaxHIB® (*Haemophilus influenzae* type b conjugate vaccine) and RECOMBIVAX HB® (Recombinant Hepatitis B vaccine) and Sanofi vaccines (Polio Vaccine Inactivated) IPOL®, five-component Acellular Pertussis Adsorbed (Pertussis Toxoid, Filamentous Haemagglutinin, Pertactin, and Fimbriae Types 2 and 3), Diphtheria Toxoid Adsorbed Bulk and Tetanus Toxoid Adsorbed Bulk Intermediates.

Applicant: MCM Vaccine Company (Sanofi Pasteur/Merck)

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1 Overview of the review

This BLA is a joint submission by the companies Merck, Sharp and Dohme, Corp and Sanofi Pasteur SA. The product is a hexavalent combination vaccine designated as PR51 and it contains six different vaccines or components of vaccine that are already approved by FDA. PR51 is composed of Merck vaccines, PedvaxHIB® (*Haemophilus influenzae* type b conjugate vaccine) and RECOMBIVAX HB® (Recombinant Hepatitis B vaccine) and Sanofi vaccines (Polio Vaccine Inactivated) IPOL®, five-component Acellular Pertussis Adsorbed (Pertussis Toxoid, Filamentous Haemagglutinin, Pertactin, and Fimbriae Types 2 and 3), Diphtheria Toxoid Adsorbed Bulk and Tetanus Toxoid Adsorbed Bulk Intermediates. These vaccine antigens are already used in other US licensed products including, Pentacel®, Diphtheria and Tetanus Toxoids Adsorbed Vaccine, DAPTACEL®, Adacel® and TENIVAC™ (STN BL 103171). PR51 is indicated for the protection against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b (Hib). Antigenic composition of PR51 is listed in Table I.

Table 1: Composition of PR51 per 0.5 mL Dose

Component	Quantity (0.5 mL dose)	Function
Diphtheria Toxoid Adsorbed ¹	15 Lf (b) (4)	Active substance
Tetanus Toxoid Adsorbed ¹	5 Lf (b) (4)	Active substance
Acellular Pertussis Antigens ¹ : Pertussis Toxoid (PT)	20 µg	Active substance
Filamentous Hemagglutinin (FHA)	20 µg	Active substance
Pertactin (PRN)	3 µg	Active substance
Fimbriae types 2, 3 (FIM)	5 µg	
Inactivated Poliomyelitis Vaccine ²		
Poliovirus Type 1(Mahoney)	29 D-Antigen Units ³	Active substance
Poliovirus Type 2 (MEF-1)	7 D-Antigen Units ³	Active substance
Poliovirus Type 3 (Saukett)	26 D-Antigen Units ³	Active substance
<i>Haemophilus influenzae</i> Type b Polysaccharide (Polyribosylribitol Phosphate [PRP]) covalently bound to 50 µg of meningococcal protein (PRP- OMPC) ⁴	3 µg	Active substance
Hepatitis B surface antigen (HBsAg) ^{4,5}	10 µg	Active substance
Aluminum phosphate	(b) (4)	Adjuvant
Aluminum hydroxyphosphate sulfate	(b) (4)	Adjuvant
Water for injection	q.s. 0.5 mL	Diluent

¹ adsorbed on aluminum phosphate

² produced in Vero cells

³ or equivalent antigenic quantity determined by a suitable immunochemical method

⁴ adsorbed on aluminum hydroxyphosphate sulfate

⁵ produced in yeast (*Saccharomyces cerevisiae*) cells by recombinant DNA technology

Note : Manufacturing Process Residuals: Per 0.5 mL dose: ≤ 50 ng bovine serum albumin, < 5 ng neomycin, ≤ 25 ng polymyxin B, < 200 ng streptomycin, (b) (4) formaldehyde, ≤ 50 ng glutaraldehyde, ≤ 0.125 µg ammonium thiocyanate, and ≤ 0.1 µg yeast protein (maximum 1% relative to HBsAg)

The safety and immunogenicity of PR5I were evaluated in each of two pivotal Phase III, randomized, active comparator controlled clinical trials that were conducted in the US (Protocols 005 and 006). These studies were conducted under the IND 14496 and are intended to support the US licensure of PR5I. Safety, tolerability and immunogenicity of PR5I when administered concomitantly with vaccines that have been licensed in the European Union (EU) were assessed in two studies conducted in the EU (Protocol 007 and 008). Studies conducted under the protocols 007 and 008 are intended to support European licensure of PR5I. Additional objectives of the overall clinical development program included the confirmation of manufacturing consistency and the evaluation of the concomitant administration of PR5I with other routine pediatric vaccines, including RotaTeq® and Prevnar 13® in the U.S. studies and ProQuad™ and Rotarix® in the EU studies.

This review covers the assays used to measure anti-pneumococcal IgG antibody concentrations in studies where the pneumococcal (Pn) vaccines Prevnar13® (13-valent) and Prevnar® (7-valent) were used concomitantly with PR5I vaccine. In three studies PR5I was administered concomitantly with Pn vaccines. Prevnar13® was used in protocols 005 and 006, while Prevnar® was used in protocol 004. In Protocol 005 immune response to Pn vaccine antigens were not measured because in this study, only the impact of potential interaction between PR5I and Prevnar13® on immune response to PR5I antigens was studied. Immune response to Pn vaccine antigens was determined in protocols 004 and 006.

2 Materials reviewed

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m.2.5. Clinical Overview

m.2.7.2. Summary of Clinical Pharmacology Studies-Merck

m.2.7.3. Summary of Clinical Efficacy

m.5.3.5.1. Study report body-v419-004 (protocol 004)

m.5.3.5.1. Study report body-v419-005 (protocol 005)

m.5.3.5.1. Study report body-v419-006 (protocol 006)

IND 618/113, ELISA used to measure antibodies against Prevnar® serotypes

(b) (4)

3 Executive summary

Serum IgG antibody responses against pneumococcal vaccines were measured in protocols 004 and 006, where pneumococcal vaccines Prevnar® (protocol 004) or Prevnar13® (protocol 005) were administered concomitantly with the investigational vaccine, PR5I. In protocol 004, Enzyme Linked Immunosorbent Assays (ELISAs) were used to measure anti-PnPS antibody levels. In this study, except serotype 18C pre-dose 4, 100% of subjects had antibodies against all 7 serotypes in both the groups above the 0.35 µg/ml threshold at all time-points tested. In protocol 006, a newly developed pneumococcal antibody detection assay, (b) (4), was used to measure antibody responses against the concomitantly administered Prevnar13® vaccine. In this protocol, other than PnPS 6B, all other serotypes met the non-inferiority criterion. For PnPS 6B, lower limit of the 2-sided 95% CI of

the GMT ratio (PR5I/control group) was 64 (less than the criterion > 67). In my opinion, given that the lower limit of the 2-sided 95% CI of the ratio for serotype 6B is close to the > 0.67 limit and the remaining 12 serotypes did meet the non-inferiority criterion, concomitant administration of PR5I and Pevnar13® appears to not interfere with the immune response to Pevnar13® serotypes. The ELISA and (b) (4) assay SOPs, validation data and assay stability data from the testing period indicated that the assay performance was satisfactory.

4 Review

4.1 Protocol 004

Protocol 004 was a Phase IIb study conducted in Canada. In protocol 004, Pevnar® was given as a concomitant vaccine to assess the potential interaction between PR5I and Pevnar®. Study 004 was a randomized open label study and contained three groups of infant subjects. In group A (n=157) subject were given PR5I concomitantly with Pevnar®. In group B (n=150) Pevnar was given one month after the administration of PR5I. In group C (n=153) Pevnar® was given concomitantly with PENTACEL™ and ENGERIX-B®. In groups A and C, Pevnar® was given at 2, 4, 6, and 15 months. In group B, Pevnar® was given at 3, 5, 7, and 16 months. Geometric mean IgG antibody titers to Pevnar® Pn serotypes were measured in groups A and C because, unlike in group B, Pevnar® was given as a concomitant vaccine in these groups. Measurement of antibodies against Pevnar® serotypes was done for information purposes only and was not included in the primary or secondary immunogenicity objectives of protocol 004. Serum anti-PnPS IgG antibody responses were measured at 28-42 days post-dose 3, immediately prior to dose 4, and 28-42 days after dose 4. ELISA measurements showed that other than serotype 18C at the pre-dose 4 time points, 100% of all subjects in both groups had antibodies against all 7 serotypes above the 0.35 µg/ml threshold on all time points. Overall, this study indicates that PR5I does not significantly interfere with the induction of antibody responses against Pevnar® serotypes.

4.1.1 IND 618, ELISA used to measure antibodies against Pevnar® serotypes

ELISAs used in the evaluation of protocol 004 response were performed by MERCK. The assays were reviewed by CBER under the IND 618. The locations of the IND 618 documents associated with PnPS ELISA were indicated in a letter of authorization submitted by the sponsor in module 1.4.1 (authorization-merck-pneumovax23) of BLA 12563/0 (Table 2).

Table 2. Location of documents related to “PnPS ELISA”

Documentation	IND / Serial / Module	Date
Validation Documentation	BB-IND 0618, Serial 0113, mod 1.11.3	29-May-2014
SOP for Assay	BB-IND 0618, Serial 0113, mod 1.11.3	29-May-2014
Data Supporting Stability of Assay	BB-IND 0618, Serial 0113, mod 1.11.3	29-May-2014

IND 618 involves the investigation of immune responses to the 23-valent Merck vaccine, Penumovax23® when administered sequentially with Pevnar13®. The Merck ELISA was first validated in 1998 at the Vaccine and Biologics Research Serology Testing Laboratory of Merck Research Laboratories in West Point, PA. The validation results covering the seven Pevnar® serotypes were submitted to FDA in 1999. In May 2002, the assay was transferred to the Vaccine and Biologics Research Serology Testing Laboratory to Merck’s clinical testing facility in Wayne, PA. Performance of the assay in the new location was confirmed through parallel testing

to assess assay concordance and precision. Although the ELISA related SOPs, validation report, and stability data were submitted to IND 618, the assays were originally evaluated as part of IND 3152, which investigated the concomitant administration of Prevnar® with a Hepatitis A vaccine. The assay went through several changes since its validation in 1998. For example,

(b) (4)

. In addition to the SOP, validation and assay stability data, IND 618 serial113 contains final validation analysis covering the changes since the initial validation. These files were previously submitted to IND 3152/452 in 2008 and were found to be satisfactory by Milan Blake. Pneumococcal ELISAs, used in BLA 125563 as part of Phase IIb study (protocol 004) were performed at the Wayne, PA facility from July 2007 through July 2008. Assay stability, covering this period, was evaluated by monitoring the performance of assay control sera (US reference serum Lot (b) (4)). According to the SOP, control serum is added to each assay plate in (b) (4). To assess stability, the geometric mean titer and the ratio of the maximum titer to the minimum titer (QC titer) for each dilution is calculated. The QC ratio and QC geometric trending for the control serum from all clinical runs performed from January 2004 through the clinical testing for protocol 004 are provided for the seven Prevnar® serotypes. The graphs show that for all serotypes, the assay has remained stable over time, no shifts or aberrant results were noted in the data, suggesting that the assay was sufficiently stable during the clinical testing for protocol 004 study.

4.2 Protocol 006

Protocol 006 was conducted as a randomized, partially double-blind, active-comparator-controlled, lot-to-lot consistency study to evaluate safety, tolerability and immunogenicity of PR5I vaccine when given concomitantly with Prevnar13® and RotaTeq®^M vaccines. In this study, immune responses to Prevnar13® were determined to assess the potential interaction between PR5I and Prevnar13®. The PR5I group (n=1256) was given PR5I, Prevnar13® and RotaTeq® at 2, 4, 6 months followed by PENTACEL® and Prevnar13® at 15 months. The control group (n=191) received PENTACEL®, Prevnar13® and RotaTeq® at 2, 4, 6 months and Recombivax HB® at 2 and 6 months followed by PENTACEL® and Prevnar13® at 15 months. Immunogenicity, as measured by geometric mean IgG antibody titer (GMT) against the concomitantly administered Prevnar13®, was evaluated as a secondary objective. The objective was to demonstrate non-inferiority of antibody responses against the 13-vaccine serotypes in Prevnar13® in the PR5I group when compared to the control group. The criterion for noninferiority was that, for each of the Prevnar13® serotypes, a lower limit of the 2-sided 95% CI of the GMT ratios (PR5I/control group) had to be > 67.

As can be seen in Table 3, other than serotypes 4 and 9V, IgG antibody concentrations against 11 serotypes were lower in PR5I group as compared to control group. Antibody levels against serotypes 4 and 9V were equivalent between the two groups. Among the 11 serotypes that elicited lower IgG antibody concentration in PR5I group, serotype 6B did not meet the non-inferiority criterion. For serotype 6B, lower limit of the 2-sided 95% CI of the GMT ratio was 0.64. Despite the failure of serotype 6B to meet the non-inferiority criterion, the sponsor concluded that the data support the concomitant use of PR5I and Prevnar13®. The sponsor argues that > 0.67 condition for the lower limit of the 2-sided 95% CI of the GMT ratio is more

stringent than the criterion used for the pivotal study used in the approval of Pevnar13®. The sponsor points out that in that study the > 0.5 criterion was used when comparing Pevnar13® immune response with Pevnar® immune response. The sponsor also indicates that the > 0.67 criterion was selected for Pevnar13® to be consistent with the > 0.67 criterion used for assessing the non-inferiority of responses to PR5I antigens. The <0.67 criterion may have been too stringent when considering previous studies of Pevnar13®. In my opinion, given that the lower limit of the 2-sided 95% CI of the ratio is close to the > 0.67 limit and the remaining 12 serotypes did meet the non-inferiority criterion, concomitant administration of PR5I and Pevnar13® appear to not interfere with the immune response to Pevnar13® serotypes.

Table 3. Analysis of Non-Inferiority Regarding GMT for Pevnar 13®Antigens at One Month Postdose 3 When Administered Concomitantly with PR5I/Control (PP-RW Population) (Protocol 006)

Antigen	PR5I group n	PR5I group Estimated GMT [1]	Control group n	Control group Estimated GMT [1]	Estimated Difference/ GMT Ratio [1] (95% CI	NI Margin	One-Sided P-Value [1]	Conclusion: Non-inferiority Criterion Met/Not Met
PN 1	1256	1.38	191	1.50	0.92 (0.82, 1.04)	0.67	<0.001	Met
PN 3	1255	0.48	191	0.51	0.95 (0.84, 1.06)	0.67	<0.001	Met
PN 4	1255	1.19	189	1.19	1.00 (0.89, 1.12)	0.67	<0.001	Met
PN 5	1256	1.42	191	1.53	0.93 (0.80, 1.07)	0.67	<0.001	Met
PN 6A	1251	2.52	191	2.89	0.87 (0.77, 0.99)	0.67	<0.001	Met
PN 6B	1255	0.96	190	1.22	0.79 (0.64, 0.96)	0.67	0.055	Not Met
PN 7F	1256	2.68	191	3.02	0.89 (0.80, 0.99)	0.67	<0.001	Met
PN 9V	1256	1.31	189	1.31	1.00 (0.88, 1.13)	0.67	<0.001	Met
PN 14	1256	4.66	191	4.90	0.95 (0.82, 1.10)	0.67	<0.001	Met
PN 18C	1253	1.57	191	1.78	0.89 (0.79, 1.00)	0.67	<0.001	Met
PN 19A	1254	1.56	191	1.71	0.91 (0.80, 1.03)	0.67	<0.001	Met
PN 19F	1256	2.14	191	2.21	0.97 (0.87, 1.08)	0.67	<0.001	Met
PN 23F	1254	1.05	190	1.16	0.90 (0.77, 1.06)	0.67	<0.001	Met

[1] The estimates for GMT, GMT ratio (PR5I Group/Control Group), and p-value are based on an ANCOVA model with natural log-transformed post vaccination titer as the response variable, and vaccination group, natural log-transformed prevaccination titer, actual brand of birth dose Hep B vaccine (RECOMBIVAX or Other/Unknown) as explanatory variables. The missing prevaccination titers are imputed by a multiple imputation method and used in the ANCOVA analysis. PR5I Group received PR5I + Pevnar 13®+ RotaTeq®at 2, 4, 6 mos; PENTACEL®+ Pevnar 13®at 15 mos. Control Group received PENTACEL®+ Pevnar 13®+ RotaTeq®at 2, 4, 6 mos, RECOMBIVAX HB®at 2, 6 mos; PENTACEL®+ Pevnar 13®at 15 mos.

ANCOVA = Analysis of covariance, CI = Confidence interval, GMT = Geometric mean titer, mos = Months, N = Number of vaccinated subjects, n = Number of subjects included in the analysis, NI = Non-inferiority, PP-RW = Per-protocol-Revised Windows (defined as vaccination window of Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to

51 following Dose 3 or the toddler dose).

In protocol 006, the IgG antibody responses against the Prevnar13® serotypes were determined using the (b) (4) assay developed by Merck. The (b) (4) assay was previously reviewed by CBER
(b) (4)

4.2.1 Review of the (b) (4) assay

(b) (4)

(b) (4)

(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4)

7 pages determined to be not releasable: (b)(4)

(b) (4)

5 Recommendations

Protocol 006 results show that PnPS 6B did not meet the non-inferiority criterion established for the concomitantly administered Prevnar13® vaccine for one of the 13 serotypes. In my opinion, given that the lower limit of the 2-sided 95% CI of the ratio for PnPS 6B (64) is close to the > 0.67 limit and the remaining 12 serotypes did meet the non-inferiority criterion, concomitant administration of PR5I and Prevnar13® appear to not interfere with the immune response to Prevnar13® serotypes.

Based on the review of the data supporting the ELISA and the (b) (4) assays used in the evaluation of serum anti-pneumococcal IgG antibody levels of individuals who received Prevnar® or Prevnar13® vaccines concomitantly with the (b) (4) the assays' performance parameters are adequate for their intended use.

I recommend the approval of BLA 125563.