DATE: August 19, 2014

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Office of Vaccine Research and Review
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

TO: Biologics License Application Submission Tracking Number # 125549/0

SUBJECT: Clinical Serology and Bioassay Review of Biologics License Application for Meningococcal Serogroup B vaccine

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

APPLICANT: Pfizer, Inc.

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1 General Information

Pfizer is seeking United States licensure of a bivalent recombinant lipoprotein 2086 (rLP2086) for active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B in individuals aged 10 through 25 years under the Accelerated Approval licensure pathway. Pfizer proposes that the initial Biologic License Application (BLA) approval would be based on the vaccine's ability to elicit serum bactericidal activity (as measured by serum bactericidal assay using human complement [hSBA]) as demonstrated in the completed Phase 2 clinical studies as a surrogate to support clinical benefit. Breadth of vaccine coverage will be confirmed postapproval based on the results of the ongoing Phase 3 studies.

The vaccine candidate, rLP2086, consists of two purified recombinant lipoprotein 2086 antigens with one protein antigen from each of the factor H binding protein (fHBP) subfamilies (A and B). The antigens are fHBP variants B01 (subfamily B) and A05 (subfamily A). The candidate bivalent rLP2086 vaccine, is a sterile liquid suspension formulated at 120 µg/dose (60 µg each subfamily) in 10 mM histidine buffer, pH 6.0, --(b)(4)-- NaCl, 0.50 mg/mL aluminum AlPO4, and polysorbate 80 ----------(b)(4)----------.

1.1 Review Identifiers and Dates

1.1.1 **Biologics License Application (BLA) Submission Tracking Number (STN)** #: 125549/0

1.1.2 **Submission received by CBER:** June 16, 2014

1.1.3 **Review completed:** August 19, 2014

1.1.4 **Material Reviewed**

The following general module sections of the BLA were reviewed:

m1	Regional
m2	Common Technical Document Summaries
m3	Quality
m4	Nonclinical Study Reports
m5	Clinical Study Reports

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

Original submissions dated 8 May 2014, 12 May 2014, 29 May, 2014 and 16 June 2014

m1.6	Meetings
m1.14	Labelling
m2.3.S	Drug Substance
	Control of Drug Substance (------*(b)(4)*-------)
	Reference Standards or Materials – Preparation and Characterization of Reference Standard (-----*(b)(4)*-----)

	Reference Standards or Materials – Qualification of Future Reference Standard (------*(b)(4)*--------)
m2.3.P	Drug Product
	Control of Drug Product (---------*(b)(4)*-------- potency)
	Reference Standards or Materials (----------*(b)(4)*--------- potency)
	Stability (potency)
m2.5	Clinical Overview
m2.7.3	Summary of Clinical Efficacy
m3.2.S.4.	Control of Drug Substance (-------*(b)(4)*--------)
m3.2.S.5	Reference Standards or Materials (----------*(b)(4)*----------)
m3.2.P.5	Control of Drug Product (----------*(b)(4)*---------- potency)
m3.2.P.6	Reference Standards or Materials (----------*(b)(4)*---------- potency)
m5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies (meningococcal bactericidal assays)
m5.3.5.1	Study Reports of Controlled Clinical Pertinant to the Claimed Indication, b1971005, b1971010, b1971011
m5.3.5.2	Study Reports of Uncontrolled Clinical Studies, b1971012
m5.3.5.3	Reports of Analyses of Data from More than One Study
	Integrated Summary of Efficacy

Amendment 3: Date Submitted: 30 May 2014

m1.11.3	Efficacy Information Amendment

Amendment 8: Date Submitted: 23 July 2014

m1.11.1	Quality Information Amendment
m3.2.P.5.3	Validation of Analytical Procedures (------*(b)(4)*-------)

1.1.5 **Related Master File, INDs and BLAs**
IND 13812

2 Executive Summary

The areas included in this review are the clinical serologic assays and clinical serology data used as the correlate of efficacy, and the following bioassays used for product release testing: the ----------*(b)(4)*---------- potency test.

Clinical serology

The benefit of the vaccine is inferred from the vaccine induced serum bactericidal activity. The relevant clinical endpoints and criteria, as well as the quality of the serum bactericidal assays using human complement (hSBA) were discussed extensively during clinical development of the vaccine. CBER and Pfizer agreed that the clinical endpoints would be based on the hSBA responses against four primary meningococcal group B strains, two from each subfamily and representing the most commonly found fHBA variant in each subfamily. In order to demonstrate sufficient responses to the vaccine components, four fold rises against each individual strain were assessed. In order to demonstrate preliminary breadth of responses, the percent of subjects

whose post vaccination titer exceeded the lower limit of quantitation (LLOQ) against all four strains tested was assessed. Finally, breadth of coverage is to be assessed by testing vaccinees' sera against additional secondary strains representing both subfamilies to verify the cross protection afforded by the vaccine. For the purposes of the accelerated approval, the data from Phase 2 studies demonstrating vaccine induced responses against the primary strains were reviewed as evidence of effectiveness. The confirmation of effectiveness using the secondary strains in Phase 3 studies will be required.

The CBER recommended clinical endpoint of four fold responses to each strain and the percent above the LLOQ for all strains was compared across all three pivotal studies (B1971010, B1971011, B1971012) where possible. The results were consistent across the three studies. The lowest response with regard to four fold response rate was that in study B1971012 against the B24 strain: 75.4% (95% CI of 70.6 to 79.8). The lowest response with regard to the percent of subjects with serum titers greater than the LLOQ against all four strains was that in study 1971011: 81.0% (95% CI of 78.0 to 83.7). The data provide reasonable evidence of the likely benefit of the vaccine.

The performance of the hSBAs was supported with validation reports and additional assay performance data that were submitted to the IND and the BLA. The performance of the assays was found to be adequate for their intended use

Product release testing

-------*(b)(4)*-------- assay

The --------*(b)(4)*------- assay -(b)(4)- is used to assess the ----------
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----------(b)(4)----------

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The (b)(4) was characterized and validated. The specifications appear to be appropriate. The test is likely adequate to detect meaningful changes to the ----------(b)(4)---------- final drug products and suitable as a release and stability test of the product.

(b)(4) potency assay

The *(b)(4)* potency assay is used to assess the potency of the final drug product. The assay uses ----------(b)(4)----------
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The potency assay was characterized and qualified. The assay will be validated when moved to the permanent product testing laboratory. The qualification data indicate that the assay is under control and able to perform adequately until fully validated. The specifications appear to be appropriate. The test is likely adequate to detect meaningful changes to the final drug product and is suitable as a release and stability test of the product.

3 Review

3.1 Clinical serology

Performance of the meningococcal serum bactericidal assays (hSBAs)

The following documents were submitted in support of the hSBAs used to assess efficacy in clinical studies. Summary information is taken from the original application Module 2.7.1, Table 1, Summary of Bioanalytical Methods for Human Studies. All documents are found in BLA Section 5.3.1.4.

Serum bactericidal assay using human complement (hSBA) for antibody to MnB strain PMB2001 (A56), VR-MVR-10017

Serum bactericidal assay using human complement (hSBA) for antibody to MnB strain PMB2001 (A56), Transfer to CRO ----------(b)(4)----------, VR-ECD-10052

Serum bactericidal assay using human complement (hSBA) for antibody to MnB strain PMB80 (A22),
VR-MVR-10026, VR-MVR-10020

Serum bactericidal assay using human complement (hSBA) for antibody to MnB strain PMB2948 (B24), VR-MVR-10024, VR-MVR-10022

Serum bactericidal assay using human complement (hSBA) for antibody to MnB strain PMB2707 (B44), VR-MVR-10019, VR-MVR-10021

Serum bactericidal assay using human complement (hSBA) for antibody to MnB strain PMB2707 (B44), Transfer to CRO ----------(b)(4)----------, VR-ECD-10053

Supplemental dilutional linearity of serum bactericidal assay using human complement (hSBA) for antibody to MnB strains PMB80 (A22), PMB2001 (A56), PMB2707 (B44), and PMB2948 (B24). VR-MVR-10129

The assay validations conducted at Pfizer were submitted to IND 13812 and reviewed prior to the start of the Phase 3 studies. After review and discussion of the data with the sponsor, CBER accepted the currently reported lower limits of quantition (LLOQs) based on the precision and

accuracy data, and agreed with the sponsor that the assays for the A22, A56, B24 and B44 strains were suitable for their intended use in Phase 3 studies. The assay transfer reports for the assays for B44 and A56 conducted ----------(b)(4)---------- were also submitted to the IND just prior to BLA submission but not formally reviewed until submission to the BLA. The study "Supplemental Dilutional Linearity Data for hSBA Validations for *Neisseria meningitidis* serogroup B strains PMB2001 (A56), PMB2707 (B44), PMB80 (A22) and PMB2948 (B24)" was not formally submitted to the IND.

Summary of the assay validations at Pfizer

Up to three reports were submitted to support the performance of each hSBA when conducted at Pfizer. Each of the four assays was subject to a validation study assessing accuracy and precision. In addition, presumably negative samples were assessed in each assay to provide data to support the use of 1:4 as the imputed value for samples with reported values at or below 1:4. Pfizer requested the use of 1:4 as a limit of detection (LOD) for imputing negative values rather than the LLOQ. Pfizer was concerned that imputing negative preimmunization values to the LLOQ would require a higher post-vaccination sample value to meet the four fold rise criterion and potentially cause the response rates to be underestimated. The evaluation of the LOD was provided in the original validation report for the assay using A56, and as a separate report for the other strains. Finally, CBER requested additional dilutional linearity data to support the accuracy of the assay using an appropriate to dilute the mock samples. The dilutional linearity data in the original validation reports was based on samples diluted in a serum substitute, ----------(b)(4)---------- that does not mimic normal human serum. Pfizer replaced the commercially available (b)(4) with a serum depleted of antibody using a -------(b)(4)-------- and repeated the dilutional linearity experiments. One report covering the four assays was submitted.

Precision was assessed using clinical samples whose antibody levels spanned the working range of the assay. Samples were tested multiple times across different days, and criteria set based on the closeness of agreement between the titers when compared to the median titer for each sample. Agreement within the replicates for a given sample, and the percentage of samples that showed acceptable precision were assessed. Based on feedback from CBER, Pfizer tested additional low titer samples to verify the precision of the assays at the proposed LLOQs. Overall the precision of the assay was demonstrated to be approximately two fold above and below the median titer as expected for bactericidal assays. The limits of quantitation were shown to be 1:16 for the assay for the A22 strain and 1:8 for the A56, B24 and B44 strains.

Accuracy was assessed using clinical samples diluted in either commercial (b)(4) or negative serum prepared by reducing nonspecific antibody using --(b)(4)--, again spanning the working range of the assay. CBER informed Pfizer that the commercially available -(b)(4)- used during the formal validations was not suitable as a serum matrix as it is composed almost completely of -------(b)(4)-------. CBER considered the ---(b)(4)--- treated serum an acceptable alternative. Pfizer provided additional data outside the validation reports on dilutional linearity of the assays using the --(b)(4)-- treated serum as the diluent. These data included samples with titers down to and below the limits of quantitation and detection. Based on all the data submitted, including multiple samples across the working range of the assay diluted in two fold series up to 8 fold, CBER confirmed that the assays were dilutionally linear down to the LLOQs.

Pfizer requested that CBER allow them to impute negative values to the lowest dilution tested (1:4), rather than to the LLOQ, for the purposes of determining fold rises. In order to support the use of the lowest dilution, Pfizer provided precision data on negative samples as well as dilutional linearity data from samples diluted down to and just below the assumed LOD. Pfizer successfully showed that negative samples were unlikely to be falsely positive in the assay, and that positive samples were subject to the expected variability of the assay at the limit of detection. The definition of four fold rise was based on the demonstrated limits of detection and quantitation.

Pfizer transferred the assays for the A56 and B44 strains to a contract research organization, ----------(b)(4)----------, concurrently with the validations performed at Pfizer. As the reagents and strains used at (b)(4) are identical to those used at Pfizer, only precision was assessed during assay transfer. Samples across the working ranges of the assays were tested at (b)(4) and shown to have the expected precision. However, only three samples with median titers of 4 or 8 were tested in the precision evaluation for the assay against the A56 strain. With regard to quantitative agreement between the laboratories, Pfizer did not formally compare the titers between the two laboratories. When comparing the sample run for each of the validations, (b)(4) samples across the range of the assay were tested in both laboratories against the B44 strain, and all titers were within a two-fold between laboratories. Of the (b)(4) samples tested in both laboratories against the A56 strain, (b)(4) were within two fold between laboratories. Insufficient samples with low titers were tested in both laboratories to demonstrate agreement at the LLOQs for the assay against the A56 strain. However, as seen with the assays performed at Pfizer, presumed negative samples were rarely positive in the assays at (b)(4) and therefore the imputation of samples less than 4 to 4 is supported.

In summary, the hSBAs performed at Pfizer are considered adequately validated for use to determine the effectiveness of the vaccine. The assays performed at (b)(4) are considered adequately validated for use in Phase 2 studies and the data generated may be considered to support a conclusion of the vaccine being reasonably likely to confer benefit. Data from the two laboratories should not be combined as insufficient data have been provided to demonstrate quantitative agreement between the laboratories.

Clinical serology data

Study B1971005 was reviewed as it provided the data to support the selection of vaccine dose. The following studies were reviewed as they generated data to demonstrate the benefit of the vaccine: B1971010, B1971011 and B1971012. The only one of these studies conducted in the U.S. was B1971011. Data generated in non US populations may not reflect responses in US subjects as the background rates of meningococcal B disease and preexisting titers may vary by geographic location. The study reports can be found in section 5.3.5 of the BLA.

Each study is listed below with a summary review.

B1971005: Stage 1 Interim Report: A Randomized, Single-Blind, Placebo Controlled, Phase 2 Trial of the Safety, Immunogenicity, and Tolerability of Meningococcal Serogroup B (MnB)

rLP2086 Vaccine At Doses Of 60 µg, 120 µg, And 200 µg in Healthy Adolescents Aged 11 to 18 Years

Primary objective: to assess the immunogenicity of 60 µg, 120 µg, and 200 µg recombinant lipoprotein 2086 (rLP2086) vaccine as measured by serum bactericidal assay with human complement (hSBA) performed with meningococcal serogroup B (MnB) strains expressing LP2086 subfamily A and B proteins in healthy adolescents aged 11 to 18 years.

All subjects received 3 intramuscular doses of 0.5 mL rLP2086 vaccine or placebo in the deltoid of the nondominant arm on a 0-, 2-, and 6- to 9-month schedule. Of the 539 subjects enrolled in the study, 22 were in the 60 µg rLP2086 vaccine group, 198 were in the 120 µg rLP2086 vaccine group, 198 were in the 200 µg rLP2086 vaccine group, and 121 were in the placebo (control) group.

The assays were not fully validated for use in this study and the LLOQs used were 1:9, 1:10, 1:18, 1:9, 1:12 and 1:7 for hSBA strains PMB1745 (A05), PMB17 (B02), PMB3302 (A04), PMB1256 (B03), PMB2001 (A56) and PMB2707 (B44), respectively.

Study Dates: 9 February 2009 to 10 May 2010 (last blood draw); 8 December 2010 (last serology completion date)

Results

The data from the study are consistent with the expected performance of the assays and no unusual results were noted.

Presented in the table below are the point estimates for the post dose 3 percent above LLOQ for each strain, modified intention-to-treat (mITT) population from Table 9-6 of the clinical study report.

Table 1 - Point estimates for the post dose 3 percent above LLOQ for each strain, modified intention-to-treat (mITT) population

Strain	Control	60 µg dose	120 µg dose	200 µg dose
A04 (PMB3302)	14.0	100.0	100	99.0
A05 (PMB1745)	11.8	90.0	97.4	96.2
A56 (PMB2001)	11.5	95.2	97.4	95.5
B02 (PMB17)	6.3	90.5	92.0	89.5
B03 (PMB1256)	7.4	53.3	75.6	67.9
B44 (PMB2707)	4.8	76.2	88.7	86.5

The data presented in the table and the reverse cumulative response curves found in Figures, 16.1 thorugh 16.12 in the clinical study report indicate that three doses induce responses in additional individuals when compared to two doses and that the maximum responses are seen in subject who receive the 120 µg dose. No benefit to increasing the dose to 200 µg was seen.

B1971010: A Phase 2, Randomized, Placebo-Controlled, Single-Blind Trial to Assess the Safety, Tolerability, and Immunogenicity of Repevax and Bivalent rLP2086 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥11 to <19 Years

The serologic data for this study were generated at Pfizer Vaccine Research – High Throughput Clinical Testing for variants A22 and B24, and -------(b)(4)------- for variants A56 and B44.

Study groups:

Group 1 received three doses of the MenB vaccine with the first dose coadministered with Repevax

Group 2 received Repevax only

Primary Objective

To demonstrate that the immune response induced by Repevax given with bivalent rLP2086 (Group 1) was noninferior to the immune response induced by Repevax alone (Group 2) when measured one month after Vaccination 1. The immune responses to all components of Repevax were assessed.

Secondary Objective

To describe the immune response as measured by hSBA performed with four primary MnB test strains, two expressing a LP2086 subfamily A protein and two expressing a LP2086 subfamily B protein, measured one month after the third vaccination with bivalent rLP2086. Serum samples from approximately 50% of the subjects had hSBA performed with test strains of LP2086 variants A22 and B24 and the other 50% were tested with strains of variants A56 and B44.

Results

The responses to Repevax are not relevant to this BLA and are not reviewed here.

The descriptions of the hSBA responses included percent of subjects above the LLOQ and other cutoffs, the geometric mean titers and the reverse cumulative distribution curves. The validated LLOQs for each assay were used. The table below summarizes the data for subjects with hSBA titer great than the LLOQ post 3rd dose in the evaluable immunogenicity population from Table 19 in the clinical study report.

Table 2 - Percent of subjects with titers ≥ LLOQ

Strain	N	%	(95% CI)
PMB80 [A22]	158	95.6	(91.1, 98.2)
PMB2001 [A56]	148	100	(97.5, 100)
PMB2948 [B24]	157	96.8	(92.7, 99.0)
PMB2707 [B44]	146	81.5	(74.2, 87.4)

Below are the reverse cumulative distribution curves for the four hSBAs from the B1971010 study body report. The top of each figure presents the curves from subjects who received the MenB vaccine; the bottom of each figure presents the curves from those who did not receive the MenB vaccine. The reverse cumulative distribution curves support a substantial response to the MenB components in the vaccine and are consistent with the expected response. Note that the pre-vaccination curves in the top graphs are consistent with the pre- and post-vaccination curves in the bottom graphs as expected.

Figure 2. Reverse Cumulative Distribution Curves, PMB80 [A22] by Study Tim
Postvaccination 3 Evaluable Immunogenicity Population

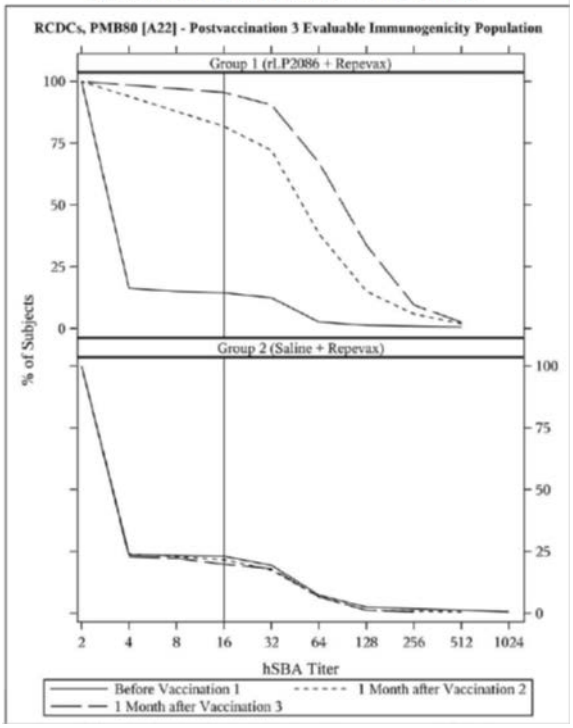


Figure 3. Reverse Cumulative Distribution Curves, PMB2001 [A56] by Study Ti
Postvaccination 3 Evaluable Immunogenicity Population

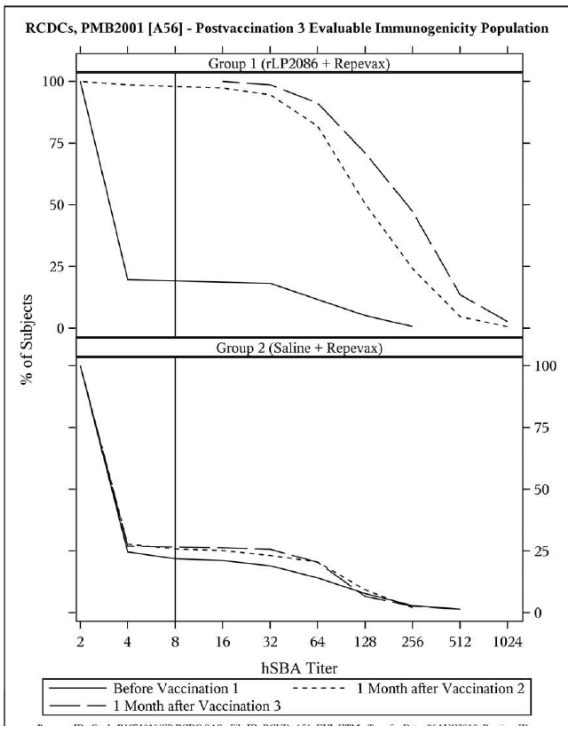


Figure 4. Reverse Cumulative Distribution Curves, PMB2948 [B24] by Study Ti
Postvaccination 3 Evaluable Immunogenicity Population

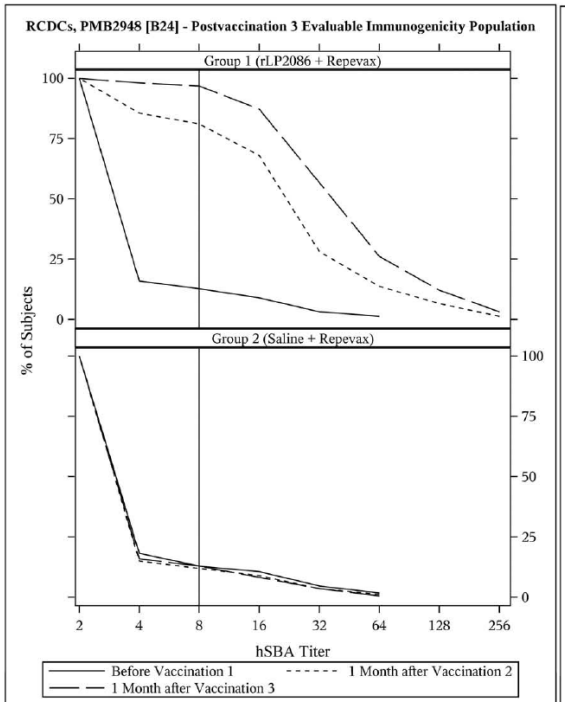
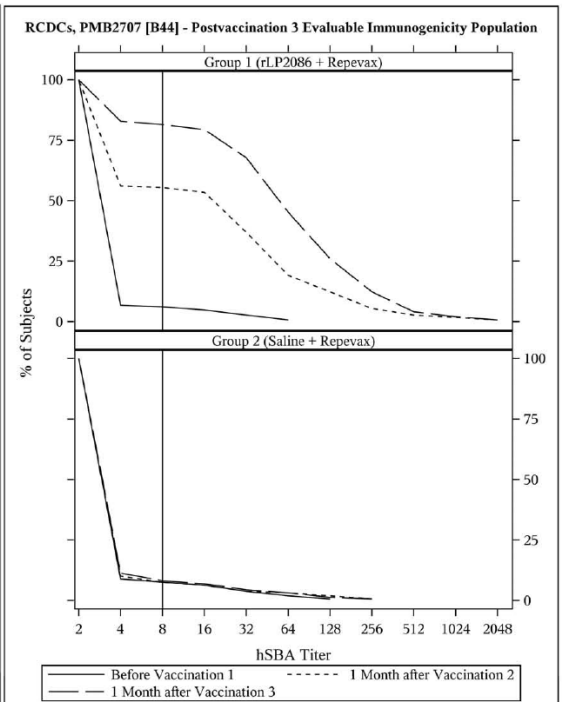


Figure 5. Reverse Cumulative Distribution Curves, PMB2707 [B44] by Study Ti
Postvaccination 3 Evaluable Immunogenicity Population



In addition to the final report, an Exploratory Serology Analyses Addendum to Final Report was submitted. In the discussions between CBER and Pfizer, agreement was reached on the Phase 3 study clinical endpoints. Four fold responses were defined based on the validated LLOQs where prevaccination values ≤ 4 were imputed to 4, prevaccination values > 4 but lower than the LLOQ were imputed to the LLOQ for the purposes of computing fold rises. In addition CBER requested the addition of a composite endpoint of the number of subjects whose post vaccination titers were greater than the LLOQ in all assays. The exploratory analyses performed in this study use the definition of fold rises recommended by CBER. The composite endpoint could not be estimated as the samples were not tested in all four of the assays.

Immunogenicity results of the exploratory analyses are presented below. The proportion of subjects achieving a ≥4-fold rise in serum bactericidal assay using human complement (hSBA) titer for each of the 4 primary *Neisseria meningitidis* serogroup B (MnB) test strains for the Postvaccination 3 evaluable immunogenicity population is presented in the table below, taken from Table 6.1, Subjects Achieving ≥4-Fold Rise in hSBA Titer – mITT Population

Table 3 - Percent of subjects with four-fold rises

Strain	**N**	**%**	**(95% CI)**
PMB80 [A22]	167	87.4	(81.4, 92.0)
PMB2001 [A56]	141	92.2	(86.5, 96.0)
PMB2948 [B24]	171	78.9	(72.1, 84.8)
PMB2707 [B44]	149	76.5	(68.9,83.1)

Overall the data support a substantive and reasonably consistent response to all strains tested in the hSBA.

Protocol B1971012: Final Report: A Phase 2, Randomized, Placebo-Controlled, Single-Blind Trial to Assess the Safety, Tolerability, and Immunogenicity of Bivalent rLP2086 Vaccine When Administered in Either 2- or 3-Dose Regimens in Healthy Subjects Aged ≥11 to <19 Years

The serologic data for this study were generated at Pfizer Vaccine Research – High Throughput Clinical Testing for variants A22 and B24, and at (b)(4) for variants A56 and B44.

Study group schedules by month:

Group 1: 0, 1, 6
Group 2: 0, 2, 6
Group 3: 0, 6
Group 4: 0, 2
Group 5: 2, 6

Primary Objectives

To assess the immune response, as measured by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins, measured 1 month after the third vaccination with bivalent rLP2086, among Group 1 subjects (0-, 1-, and 6-month vaccine schedule)
To assess the immune response, as measured by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins, measured 1 month after the third vaccination with bivalent rLP2086, among Group 2 subjects (0-, 2-, and 6-month vaccine schedule)

Secondary Objectives

To assess the immune response, as measured by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins, measured 1 month after the second vaccination with bivalent rLP2086, among Group 3 subjects (0- and 6-month vaccine schedule)
To describe the immune response, as measured by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins, throughout the study (all groups)

Results

The proposed schedule for the MenB vaccine is doses given at 0, 2 and 6 months. This review focuses on the data from that schedule, the data from Group 2.

The results are analyzed using the validated LLOQ of 8 for the assays against strains A56, B24 and B44. The analysis in was performed using an LLOQ of 8 for the assay against strain A22 however the validated LLOQ for that assays is 16. When the data for the assay against A22 were examined, minimal data between 4 and 16 were seen in the prevaccination data and none in the post last dose data. The reanalysis of the data using 16 rather than 8 as the LLOQ would have no substantive impact on the results for this study.

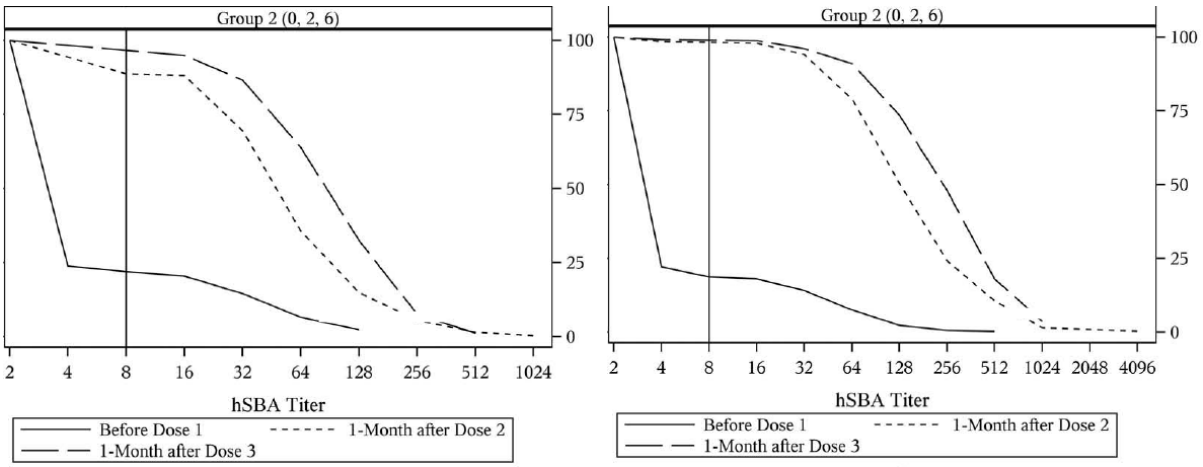
Study injections for this study were temporarily paused on 01 July 2011 during investigation of an adverse event identified for a 15-year-old female subject. The study pause caused a delay in some subjects' attending vaccination visits, resulting in these subjects' not being able to meet their originally intended dosing schedule. The study was restarted following the implementation of a substantial protocol amendment, which extended the dosing visit windows to allow subjects impacted by the delay to remain in the study. For Group 2 the number of subjects included in the "evaluable population" was 360, while the number of subject included in the "per schedule population" was 165. Analyses using both sets of data were compared to determine if the loss of subjects affected the overall outcomes. An example of the changes to the data is provided below. These data are from Tables 15 and 16 of the clinical study report, proportion of subjects achieving hSBA titers ≥ LLOQ for each primary strain.

Table 4 - Comparison of "evaluable population" versus "per schedule population"

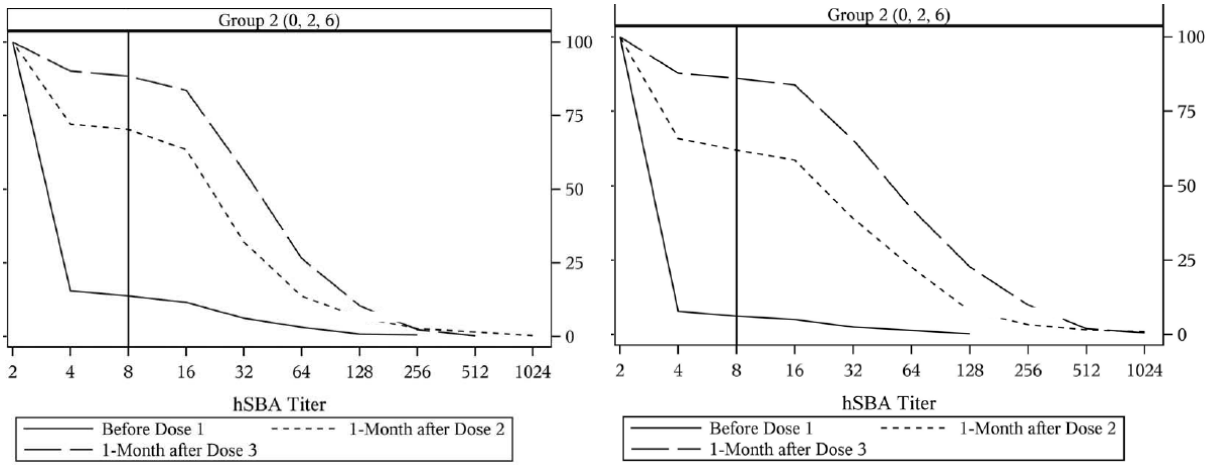
Strain	**N Evaluable population**	**% Evaluable population**	**95% CI Evaluable population**	**N Per-schedule population**	**% Per-schedule population**	**95% CI Per-schedule population**
PMB80 [A22]	357	95.0	91.7, 97.2	165	97.6	93.3, 99.5
PMB2001 [A56]	359	98.9	96.9, 99.8	165	98.2	94.2, 99.7
PMB2948 [B24]	354	88.4	84.1, 91.9	163	90.8	84.4, 95.2
PMB2707 [B44]	352	86.1	81.4, 90.0	161	83.9	76.3, 89.8

Below are the reverse cumulative distribution curves for the four hSBAs from the B1971012 study body report. The curves for the the evaluable and per-schedule populations are comparable. The curves for the evaluable population are presented. The reverse cumulative distribution curves support a substantial response to the MenB components in the vaccine and are consistent with the expected response.

PMB80 [A22] on left with PMB2001 [A56] on right (from figures 14.1 and 14.5, respectively). Percent of subjects shown on the y axis.



PMB2948 [B24] on left with PMB2707 [B44] on right (from figures 14.9 and 14.13, respectively). Percent of subjects shown on the y axis.



In addition to the final report, a Serology (or Exploratory Serology Analyses) Addendum to Final Report was submitted. As stated previously in this memo, CBER and Pfizer reached an agreement on the Phase 3 study clinical endpoints. Four fold responses were defined based on the validated LLOQs where prevaccination values ≤ 4 were imputed to 4 and prevaccination values > 4 but lower than the LLOQ were imputed to the LLOQ for the purposes of computing fold rises. In addition CBER requested the addition of a composite endpoint of the number of subjects whose post vaccination titers were greater than the LLOQ in all assays. The exploratory analyses performed in this study use the definition of fold rises recommended by CBER. Immunogenicity results of the exploratory analyses are presented below. The exploratory analysis was initially

performed using an LLOQ of 8 for all assays but then the data were reanalyzed using 16 as the LLOQ for the assay against the A22 strain.

Table 5 - Percent of subjects with four-fold rises for the 0, 2, 6 month schedule (from Table 6.19 for per-schedule and from Table 6.20 for evaluable populations)

Strain	N Evaluable population	% Evaluable population	95% CI Evaluable population	N Per-schedule population	% Per-schedule population	95% CI Per-schedule population
PMB80 [A22]	349	84.0	79.7, 87.6	167	87.4	81.4, 92.0
PMB2001 [A56]	347	94.2	91.2, 96.4	165	93.3	88.4, 96.6
PMB2948 [B24]	350	75.4	70.6, 79.8	165	78.2	71.1, 84.2
PMB2707 [B44]	349	81.7	77.2, 85.6	164	78.0	70.9, 84.1

The results of the composite analysis of the percentage of subjects who reached titers ≥ the LLOQ in all assays are also from Tables 6.19 and 6.20. For the evaluable population, N = 345 and the percent = 81.7 (95%CI 77.3, 85.7). For the per-schedule population, N = 164 and the percent = 81.7 (95%CI 74.9, 87.3).

B1971011: A Phase 2, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of Gardasil (HPV) Vaccine and Bivalent rLP2086 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥11 to <18 Years

The serologic data for this study were generated at Pfizer Vaccine Research – High Throughput Clinical Testing for variants A22 and B24, and at (b)(4) for variants A56 and B44.

Study groups (0, 2, 6 month schedule):

Group 1 received three doses of the MenB vaccine coadministered with Gardasil
Group 2 received three doses of the MenB vaccine
Group 3 received three doses of Gardasil

Coprimary Immunogenicity Objectives

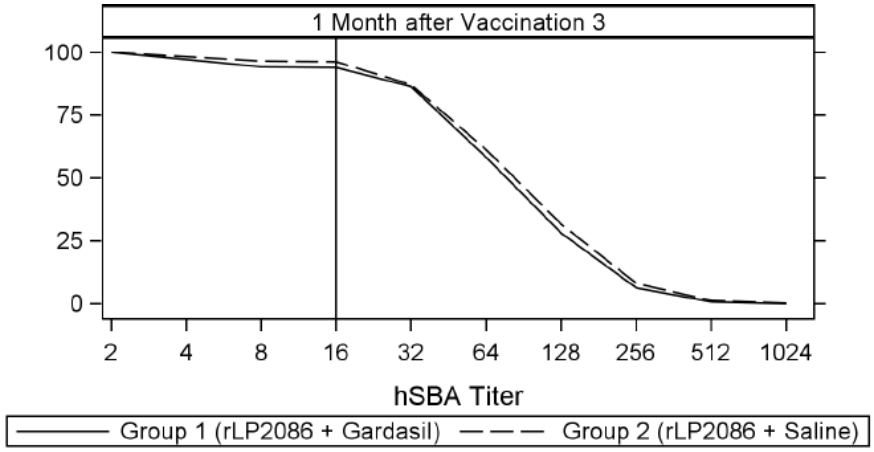
To demonstrate that the immune response (based on geometric mean titer [GMT]) induced by Gardasil given with bivalent rLP2086 (Group 1) was noninferior to the immune response induced by Gardasil alone (Group 3) as measured 1 month after the third vaccination (Visit 5) with Gardasil in both groups. The immune responses to all 4 components of Gardasil were assessed.
To demonstrate that the immune response (based on GMT) induced by bivalent rLP2086 given with Gardasil (Group 1) was noninferior to the immune response induced by bivalent rLP2086 alone (Group 2) as measured by hSBA performed with 2 MnB test strains, 1 expressing LP2086 subfamily A and 1 expressing

LP2086 subfamily B proteins, when measured 1 month after the third vaccination (Visit 5) with bivalent rLP2086 in both groups.

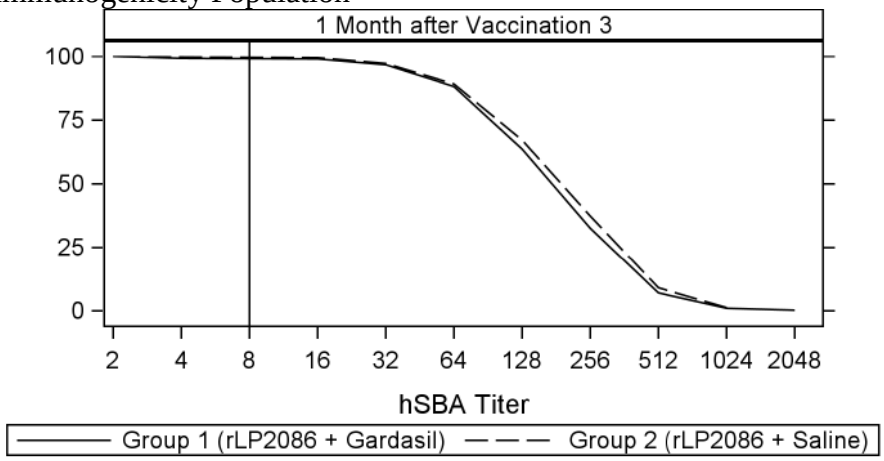
Results

The reverse cumulative distribution curves for the four hSBAs taken from the B1971011 clinical study report are below. The y axes are the percent of subjects with that titer or higher. The curves for the evaluable population are presented. The reverse cumulative distribution curves support a substantial response to the MenB components in the vaccine and are consistent with the expected response.

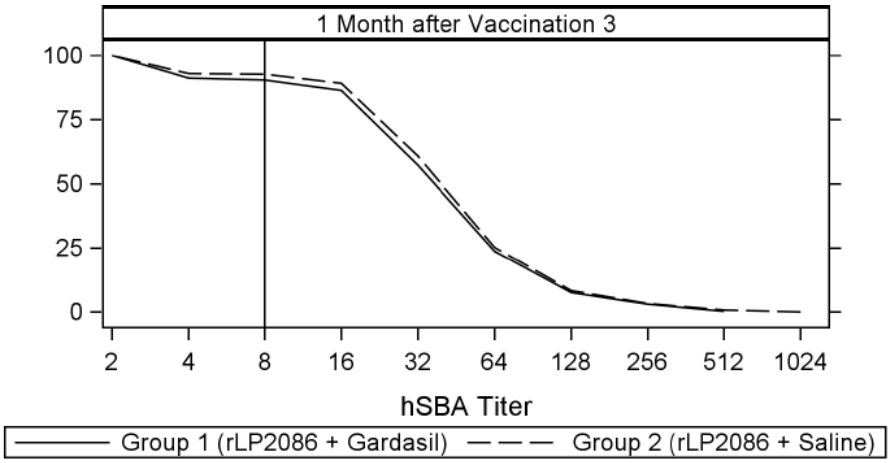
From Figure 14.1 Reverse Cumulative Distribution Curve, PMB80 [A22], Evaluable Immunogenicity Population



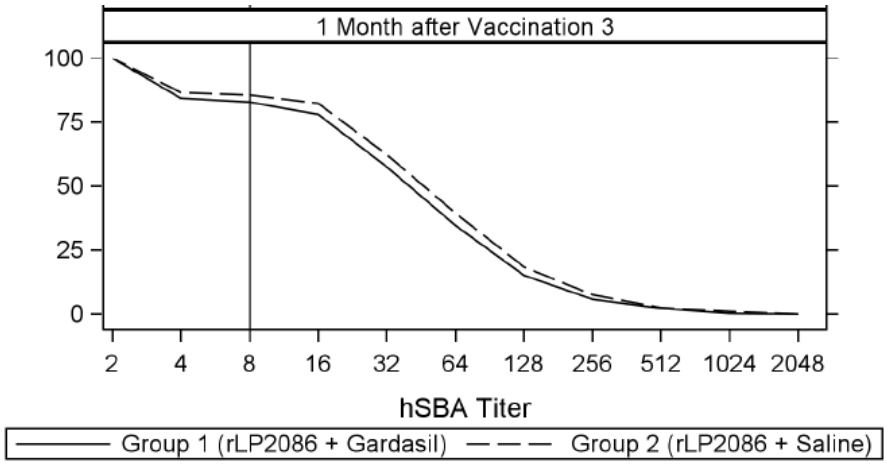
From Figure 14.2. Reverse Cumulative Distribution Curve, PMB2001 [A56], Evaluable Immunogenicity Population



From Figure 14.3. Reverse Cumulative Distribution Curve, PMB2948 [B24], Evaluable Immunogenicity Population



From Figure 14.4. Reverse Cumulative Distribution Curve, PMB2707 [B44], Evaluable Immunogenicity Population



Overall the data support a substantive and reasonably consistent response to all strains tested in the hSBA.

As an exploratory analysis, Pfizer also determined the subjects meeting the endpoints recommended by CBER: the percent achieving a four fold rise as defined by CBER, and the percent reaching the composite result of post vaccination titers greater than the LLOQ for all four strains. The post third vaccination results for the two groups receiving the MenB vaccine are tabulated below.

Table 6 - Post third vaccination results for the two groups receiving the MenB vaccine

Variant	Group 1 N	Group 1 %	Group 1 CI	Group 2 N	Group 2 %	Group 2 95% CI
A22	783	85.3	82.6-87.7	788	86.4	83.8-88.7
A56	742	95.0	93.2-96.5	730	95.3	93.6-96.8
B24	775	83.4	80.5-85.9	774	84.8	82.0-87.2
B44	792	77.0	73.9-79.9	788	80.7	77.8-83.4
Composite	751	81.0	78.0-83.7	763	83.9	81.1-86.4

Clinical review summary

The CBER recommended clinical endpoint of four fold responses to each strain and the composite response of percent above the LLOQ for all strains was compared across all three pivotal studies (B1971010, B1971011, B1971012) where possible. The results were consistent across the three studies. The data provide reasonable evidence of the likely benefit of the vaccine.

3.2 CHEMISTRY, MANUFACTURING AND CONTROL

---*(b)(4)*--

Method

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(b)(4) Final Drug Product Potency Test

During product development, CBER requested that Pfizer implement an *(b)(4)* potency test for release of drug product due to the presence of aluminum in the FDP. While aluminum is added to the FDP as a ----------(b)(4)----------, no other test characterizing the quality of the proteins in the FDP was proposed by Pfizer. Other proposed tests required the removal of the aluminum before analysis.

The ----(b)(4)---- potency assay (b)(4) is used to determine the immunogenicity of the bivalent rLP2086 drug product. --(b)(4)--.

---(b)(4)--.

The assay has been qualified but not validated at the final testing facility. Data from developmental studies were submitted supporting the selection of the ----(b)(4)---, vaccination schedule, dose, and group size. Pfizer developed a serum bactericidal assay to assess the immune responses in the (b)(4), selecting the optimum single dilution of each serum to be run to determine seropositivity. The assay appears to be capable of distinguishing a (b)(4) dose of vaccine from a full dose based on group size experiments.

1 page redacted (b)(4)

4 Recommendation

The clinical serologic assays appear to be adequate for their intended use. The immunogenicity data indicate that the vaccine is likely to provide benefit with regard to protection against meningococcal disease.

The -------*(b)(4)*------- assay and the --*(b)(4)*-- potency assay appear to be appropriate as part of the overall control of the ---------(b)(4)--------- drug product. The assays appear to be performing adequately for their intended purposes. The specifications appear to be appropriately set. The validation report for the *(b)(4)* potency assay should be submitted when available.

Based on the data I reviewed, I recommend approval of the product.