Application Type	BLA
STN	125549/0
CBER Received Date	June 16, 2014
PDUFA Goal Date	February 14, 2015
Division / Office	DB/OBE
Committee Chair	Drusilla Burns, Ph.D.
Clinical Reviewer(s)	Lucia Lee, M.D.
Project Manager	Michael Smith, Ph.D., Theodore Garnett, Ph.D. Ramachandra Naik, Ph.D.
Priority Review	Breakthrough Therapy
Reviewer Name(s)	Tsai-Lien Lin, Ph.D. Lead Mathematical Statistician
Review Completion Date / Stamped Date	
Supervisory Concurrence	A. Dale Horne, Dr.P.H. Branch Chief, VEB, DB
	Estelle Russek-Cohen, Ph.D. Division Director, DB, OBE
Applicant	Pfizer
Established Name	Neisseria meningitidis Serogroup B bivalent rLP2086 vaccine
(Proposed) Trade Name	Trumenba
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Sterile liquid suspension of 60 μg of subfamily A and 60 μg of subfamily B rLP2086 (120 μg total protein) per 0.5 mL dose
Dosage Form(s) and Route(s) of Administration	0.5 mL single-dose pre-filled syringes with 60 μg of subfamily A and 60 μg of subfamily B rLP2086 (120 μg total protein) per 0.5 mL dose, to be injected intramuscularly
Dosing Regimen	3-dose series on a 0, 2, and 6 month schedule
Indication(s) and Intended Population(s)	Active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B in individuals aged 10 through 25 years

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1. Executive Summary

This assay statistical review focuses on two bioassays related to product potency that are used for release and stability testing: the ----------(b)(4)--------- and the (b)(4) potency test (b)(4), and the clinical serologic assay: the serum bactericidal assay using human complement (hSBA).

CMC Release testing:

The (b)(4) assay is used to assess the ------(b)(4)----- at -------(b)(4)--------- final drug product stages. The assay appears to be precise, accurate, and linear over the assay range. The proposed (b)(4) specifications appear to be acceptable.

The (b)(4) assay is a ----------(b)(4)------ assay and is used to assess the potency of the final drug product. The assay was qualified, but has not been validated yet. The qualification data showed that although the (b)(4) assay has large variability, which is typical for a biological assay, its performance may be adequate and will be confirmed when fully validated. The proposed tolerance interval derived (b)(4) specifications appear to be very wide due to the limited number of lots available. The applicant will re-evaluate and appropriately adjust the specifications after testing an additional (b)(4) commercial lots at release.

Clinical Serologic Assay:

The serum bactericidal assay using human complement (hSBA) measures serum bactericidal activity, which serves as the immunological surrogate for vaccine efficacy. The selection of four primary strains for hSBA testing and the validation of hSBA assays have been extensively discussed between CBER and Pfizer under IND 13812. The hSBA assay performs adequately for the intended use, based on the validation data submitted.

2. Clinical and Regulatory Background

Pfizer submitted BLA 125549/0 to seek licensure of a bivalent recombinant lipoprotein 2086 (rLP2086) vaccine for active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B in individuals aged 10 through 25 years under the Breakthrough Therapy pathway.

The rLP2086 vaccine candidate consists of two purified recombinant lipoprotein 2086 antigens (A05 and B01) with one protein antigen from each of the factor H binding protein (fHBP) subfamilies (A and B). The candidate bivalent rLP2086 vaccine is a sterile liquid suspension formulated at 120 μg/dose (60 μg each subfamily) in 10 mM histidine buffer.

To support the efficacy of rLP2086, the immunological surrogate, serum bactericidal activity, as measured by serum bactericidal assay using human complement was used. The 4 strains selected as the primary test strains (A22, A56, B24, and B44) in hSBA

assays and the validation of hSBA assays for these 4 primary strains have been extensively discussed and reviewed under IND 13812.

Two bioassays related to product potency are proposed for release testing: the ----------(b)(4)---------- and the ----(b)(4)---- potency test ((b)(4)). The (b)(4) is used to assess the ------(b)(4)----- at the --------(b)(4)---------- the final drug product stages, but cannot be considered a potency test of the final drug product. The (b)(4) was characterized and validated. The (b)(4) potency assay is used to assess the potency of the final drug product. The potency assay was characterized and qualified, but not validated yet.

5. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This statistical review focuses on the two assays for release testing (the (b)(4) and the (b)(4) assay), which have not been reviewed by the agency prior to the BLA submission. The review also covers the hSBA assays used to support the clinical studies.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

BLA 125549/0.2 Submitted 5/29/2014

- Module 2.3 Quality Overall Summary
  - 2.3.S.4 Control of Drug Substance
  - 2.3.P.5 Control of Drug Product
- Module 3. Quality
- Module 3.2.S. Drug Substance
  - 3.2.S.4.2 Analytical Procedures ----------(b)(4)----------
  - 3.2.S.4.3 Validation of Analytical Procedures ---------(b)(4)----------
- Module 3.2.P. Drug Product
  - 3.2.P.5.2. Analytical Procedures --------(b)(4)----------
  - 3.2.P.5.2. Analytical Procedures --(b)(4)--Potency
  - 3.2.P.5.3 Validation of Analytical Procedures – -----(b)(4)----------
  - 3.2.P.5.3 Validation of Analytical Procedures – Qualification of the (b)(4) Potency Assay

BLA 125549/0.8 Submitted 7/23/2014

Response to 24 June 2014 CBER Questions
- 3.2.P.5.3 Validation of Analytical Procedures – ----------(b)(4)---------- (revised)

BLA 125549/0.0 Submitted 5/8/2014

- Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
- Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

VR-MVR-10024 Validation Report of hSBA for MenB Strain PMB2948 (B24)
VR-MVR-10019 Validation Report of hSBA for MenB Strain PMB2707 (B44)
VR-MVR-10017 Validation Report of hSBA for MenB Strain PMB2001 (A56)
VR-MVR-10026 Validation Report of hSBA for MenB Strain PMB80 (A22)
VR-MVR-10129 Supplemental Dilutional Linearity Data for hSBA Validation for MenB Strains A56, B44, A22, and B24
VR-MVR-10020 Validation Report for the Limit of Detection and False-Positive Rate of hSBA for MenB Strain PMB80 (A22)
VR-MVR-10021 Validation Report for the Limit of Detection and False-Positive Rate of hSBA for MenB Strain PMB2707 (B44)
VR-MVR-10022 Validation Report for the Limit of Detection and False-Positive Rate of hSBA for MenB Strain PMB2948 (B24)
VR-ECD -10052 Transfer Validation of Assay Performance (Precision) of hSBA for Detection of Functional Antibodies to MenB Strain PMB2001
VR-ECD -10053 Transfer Validation of Assay Performance (Precision) of hSBA for Detection of Functional Antibodies to MenB Strain PMB2707

6. DISCUSSION OF INDIVIDUAL ASSAYS

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

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

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

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

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Reviewer Comments:

The analysis of linearity (regression of observed versus expected concentrations) was originally performed on the untransformed scale. It was noted that the variance increases with the increasing concentration, suggesting that an analysis on the log-transformed scale would be more appropriate. In addition, the applicant reported slope, intercept, and R^2 without pre-specified acceptance criteria. An Information Request (IR) was sent to the applicant on 6/24/14, requesting the regression analysis be performed on the log-transformed scale and the 95%CI of the slope and intercept be reported.

The 6/24/14 IR also included a request for clarification. DP linearity data presented in Tables 9 and 10 on page 15 of the validation report of the ---------(b)(4)---------- for MnB RLP2086 Drug Product do not match the linearity data displayed in Figures 1 and 2 (page 16). The applicant was also asked to explain why a variance component analysis for DP intermediate precision was not performed, although the experimental design permitted such an analysis.

Submitted to Amendment 8 in response to the 6/24/14 IR, the applicant re-analyzed the linearity data on the log-transformed scale and provided detailed model diagnostics supporting the analysis on the log scale as the appropriate analysis. The validation reports were updated. The DP linearity data in Tables 9 and 10 of the DP validation report were corrected. The applicant also performed a variance component analysis to estimate the intermediate precision for each DP dose (120 µg or 200 µg) at each lab (----------(b)(4)----------). The %GCV ranges from ---------(b)(4)---------- and from ----------(b)(4)----------, similar to the results reported in the validation reports.

The applicant's responses to these IR questions are satisfactory. The (b)(4) assay appears to be precise, accurate, and linear over the assay range. The linearity results submitted in Amendment 8 have been incorporated in Tables 1 and 2 below.

2 pages determined to be not releasable

The (b)(4) Specifications

Tolerance intervals with 95% confidence and 99% coverage based on (b)(4) commercial scale (b)(4) batches and (b)(4) commercial scale DP batches (including (b)(4) batches used in clinical studies) are calculated and further narrowed or adjusted by the specifications already established for phase 3 clinical material manufactured at commercial scale. The specification is set at ----------(b)(4)----------.

Reviewer Comments:

The strategy used for setting the specifications follows what was agreed upon in the pre-BLA meeting. The proposed specifications appear to be acceptable.

6.2 –(b)(4)---Potency (b)(4) Assay for Drug Product

The (b)(4) potency assay was used as a characterization test for clinical lots and will be used as a release and stability assay for commercial lots. The (b)(4) assay ----------(b)(4)----------. A qualification report was submitted to the BLA to support the use of this assay. However, formal validation is not completed yet.

The (b)(4) assay

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

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

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

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Reviewer Comments:

Tolerance intervals can be very wide when the number of data points is small and the variability is large. The tolerance intervals calculated from (b)(4) lots are much wider than the data range (----------(b)(4)----------) due to considerable uncertainty from a small sample size. The variability of a biological assay is usually large, especially for a quantal assay. The (b)(4) assay variability as it is now is quite large, ----(b)(4)----------, although the qualification report shows that it has been optimized in many aspects. Whether it is feasible or efficient to have a continuous response in the assay (---(b)(4)-------), instead of the qualitative ---(b)(4)---- response, is not known. The use of --------(b)(4)---------- assay was originally proposed to be used only for characterization of the DP, not as a release test. The (b)(4) assay will be re-evaluated when the validation report is submitted. With the currently proposed specifications, the assay is able to detect substantial losses in potency of the drug product.

6.3 Serum Bactericidal Assays Using Human Complement (hSBA)

The hSBAs were used to assess efficacy in clinical studies. The validations of hSBAs for the four primary strains (A22, A56, B24, and B44) were submitted and reviewed under IND 13812 prior to the start of Phase 3 studies. The currently reported LLOQs, which are used in defining the immunogenicity endpoints in Phase 3 studies and are determined based on the precision and relative accuracy data presented in the validation reports conducted at Pfizer, have been agreed to by CBER. The assay transfer reports for strains A56 and B44 conducted at ----------(b)(4)----------), which were submitted to the IND just prior to BLA submission, have not yet been formally reviewed. The Supplemental Dilutional Linearity Data for hSBA Validations for MenB strains A56, B44, A22, and B24 were not formally submitted to the IND.

The hSBA Assay

----------(b)(4)----------
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1 page determined not to be releasable

The LLOQs agreed to by CBER are 1:16 for the assay for strain A22 and 1:8 for strains A56, B24, and B44.

Reviewer Comments:

The acceptance criteria used for assessing dilutional linearity and precision, which are based on proportions, do not have as desirable statistical properties as a more quantitative criterion would have. It does not have as much power to differentiate a good assay from a poor assay. The relative accuracy/dilutional linearity criterion also does not address the appropriate statistical question; it is not sensitive to bias. Since this type of acceptance criterion is based on proportions, it requires a larger sample size to make the estimated proportion reliable enough, and is therefore less efficient than a quantitative criterion would be. Despite these limitations, the validation data do show that the MenB hSBA assay performs adequately for the intended use.

Limit of Detection (LOD)

Because Pfizer requested to define the 4-fold rise endpoint by replacing the negative baseline values with the LOD 1:4, instead of LLOQ (i.e., a post-vaccination titer of ≥16 is considered as a fold-rise responder, if the baseline titer is below LOD). Therefore, additional validations were performed for the LOD. Assumed negative samples were tested multiple times. False positive rates were reported.

Reviewer Comments:

Because low titers are more likely to be baseline titers and a more relaxed definition for 4-fold rise will be used when the baseline titer is <LOD, demonstration of a low false-negative rate for titer levels ≥ 1:8 is needed. A high false-negative rate may lead to a higher chance of inflating the estimated % of subjects achieving 4-fold rise. The false negative rates were not formally evaluated. Based on the data provided in the study report "Supplemental Dilutional Linearity Data for hSBA Validations for Neisseria meningitides serogroup B Strains PMB2001 (A56), PMB2707 (B44), PMB80 (A22) and PMB2948 (B24)," the false negative rate may be higher than acceptable at titer level 1:8, especially for the A22 strain. However, since generally few baseline titers are expected to be positive and the use of a 4-fold rise endpoint may be conservative given that the "established" correlate of protection is 1:4, the reviewer does not consider lacking evidence of low false negative rate a critical concern for the use of this assay to assess efficacy of the bivalent rLP2086 vaccine.

The Transfer Validation at ----------(b)(4)----------

The MenB hSBA was developed and validated at Pfizer Vaccine Research lab. (b)(4) is a contract research lab engaged to test clinical study samples. The transfer validations for the assays for strains A56 and B44 are intended to confirm the successful transfer from Pfizer to (b)(4). Only the precision of the hSBA performed in (b)(4) facility is assessed.

----------(b)(4----------. The same precision acceptance criteria as for the validation at Pfizer lab were used. All pre-specified acceptance criteria were met.

Reviewer Comments:

Only (b)(4) samples in the low titer range (1:4 to 1:16) for strain A56 were tested for precision evaluation -- too few to apply the acceptance criterion. The transfer validation is very limited in scope. Comparability between the Pfizer lab and (b)(4) lab was not evaluated. The assays at (b)(4) may be considered adequately validated for use in Phase 2 studies. If pooling data from two laboratories or comparing results obtained from two different laboratories are desired, a well designed bridging study would be needed.

10. CONCLUSIONS AND RECOMMENDATIONS

CMC Release testing:

Two bioassays related to product potency are proposed for release testing: the -----(b)(4)----------- final drug product, and the ---*(b)(4)* potency test ((b)(4)) for final drug product.

The (b)(4) assay is used to assess the -------(b)(4)-------. The assay appears to be precise, accurate, and linear over the assay range. The proposed (b)(4) specifications appear to be acceptable.

The (b)(4) assay is a ----------(b)(4)---------. The assay was qualified, but has not been validated yet. The qualification data showed that although the (b)(4) assay has large variability, which is typical for a biological assay, its performance may be adequate and will be confirmed when fully validated. The proposed tolerance interval derived (b)(4) specifications appear to be very wide due to the limited number of lots available. The applicant will re-evaluate and appropriately adjust the specifications after testing an additional (b)(4) commercial lots at release.

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