

Application Type	Original BLA
STN	125770/0
CBER Received Date	October 21, 2022
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Division / Office	OVR
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Product Reviewer	Kathryn Matthias
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Pfizer Ireland Pharmaceuticals
Established Name	Meningococcal Groups A, B, C, W, and Y Vaccine (MenABCWY)
Trade Name	PENBRAYA®
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	After reconstitution, a single dose of 0.5 mL contains 5ug each of meningococcal serogroup A, C, W, and Y polysaccharides individually conjugated to tetanus toxoid [TT] (total 44 ug TT), 60 ug meningococcal B fHbp subfamily A, 60 ug meningococcal B fHbp subfamily B, and 0.25 mg aluminum as AlPO ₄
Dosage Form and Route of Administration	Suspension, intramuscular
Dosing Regimen	Administer 2 doses (approximately 0.5 mL each) 6 months apart
Indication and Intended Population	Active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by <i>Neisseria meningitidis</i> groups A, B, C, W, and Y

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GLOSSARY

BLA	biologics license application
CV	coefficient of variation
(b) (4)	(b) (4)
fHBP	factor H binding protein
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
IR	information request
LLOQ	lower limit of quantitation
IgG	Immunoglobulin G
IM	intramuscular
IND	Investigational New Drug application
LOD	limit of detection
MenA	meningitidis serogroup A
MenACWY	meningococcal serogroups A, C, W, and Y
menB-fHbp	meningococcal group B factor H binding protein
MenC	meningitidis serogroup C
MenW	meningitidis serogroup W
MenY	meningitidis serogroup Y
MnB	meningococcal serotype B
ULOQ	upper limit of quantitation
(b) (4)	(b) (4)

1. Executive Summary

Pfizer Ireland Pharmaceuticals (Pfizer) submitted an original Biologics License Application (BLA) on October 21, 2022 for Meningococcal Groups A, B, C, W, and Y Vaccine (MenABCWY). The proposed indication is active immunization to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age. The proposed dosage and administration route are 2 doses (approximately 0.5 mL each) via intramuscular (IM) injection 6 months apart.

This memo focuses on the statistical review of clinical immunogenicity assays of this BLA, i.e., serum bactericidal assays using human complement (hSBAs). The validation reports of the hSBAs against *Neisseria meningitidis* serogroup B strains have been reviewed during the approval of BLA125549 for Trumenba®. Hence, this review memo covers validation reports of the hSBAs against *Neisseria meningitidis* serogroup A (MenA) strain F8238, serogroup C (MenC) strain C-11, serogroup W (MenW) strain MP01240070, and serogroup Y (MenY) strain S-1975 submitted in Module 5.3.1.4 of BLA125770/0.0 and BLA125770/0.13 and the specificity reports of these assays submitted in Module 5.3.1.4 of BLA125770/0.7 and BLA125770/0.16, which have not been reviewed by a statistical reviewer previously.

The validation results demonstrated acceptable accuracy and precision in the assay ranges for each of the anti-MenACWY hSBAs. The lower and upper limits of quantitation (LLOQ and ULOQ) were determined to be (b) (4) and (b) (4) for anti-MenA and anti-MenC

hSBAs and (b) (4) and (b) (4) for anti-MenW and anti-MenY hSBAs. The limit of detection (LOD) was determined to be (b) (4) for all anti-ACWY hSBAs.

The specificity results showed that for each of the anti-MenACWY hSBAs, competition with heterologous MenACWY polysaccharides, irrelevant meningococcal B proteins (b) (4) -A and (b) (4) -B), and irrelevant pneumococcal polysaccharides resulted in minor hSBA titer (b) (4). When competed with homologous polysaccharides, all (b) (4) serum samples tested per serogroup showed a (b) (4) in titer at (b) (4) or more competitor concentrations, except for MenC, where (b) (4) out of (b) (4) serum samples tested showed a (b) (4) in titer at (b) (4) or more competitor concentrations. Based on discussion with the assay reviewer, Dr. Kathryn Matthias, some serum samples may have residual bactericidal antibodies at the lower concentrations that may still be sufficient to induce killing; thus, it is not uncommon to observe one or two samples that are not inhibited in the presence of even the highest concentration of homologous antigen. As such, the specificity results are acceptable for the anti-MenACWY hSBAs.

In conclusion, I consider the anti-MenACWY hSBAs adequate for their intended uses in support of this BLA.

2. Regulatory Background

The original Investigational New Drug Application (IND17319) for MenABCWY was submitted on February 3, 2017. Pfizer submitted this original BLA on October 21, 2022 for MenABCWY for the prevention of invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age.

The following documents regarding clinical immunogenicity assays were submitted in Module 5.3.1.4 of BLA125770/0.0:

- Validation Report of Serum Bactericidal Assay for *Neisseria meningitidis* Serotype B Strain PMB2001 (A56) (VR-MVR-10017, Version 3.0),
- Validation Report of Serum Bactericidal Assay Using Human Complement (hSBA) for Meningococcal Serotype B (MnB) Strain PMB80 (A22) (VR-MVR-10026, Version 2.0),
- Validation Report for the Limit of Detection and False-Positive Rate of Serum Bactericidal Assay for *Neisseria meningitidis* Serotype B Strain PMB80 (A22) (VR-MVR-10020, Version 4.0),
- Validation Report of Serum Bactericidal Assay Using Human Complement (hSBA) for Meningococcal Serotype B (MnB) Strain PMB2948 (B24) (VR-MVR-10024, Version 2.0),
- Validation Report for the Limit of Detection and False-Positive Rate of Serum Bactericidal Assay for *Neisseria meningitidis* Serotype B Strain PMB2948 (B24) (VR-MVR-10022, Version 4.0),
- Validation Report of Serum Bactericidal Assay Using Human Complement (hSBA) for Meningococcal Serotype B (MnB) Strain PMB2707 (B44) (VR-MVR-10019, Version 3.0),

- Validation Report for the Limit of Detection and False-Positive Rate of Serum Bactericidal Assay for *Neisseria meningitidis* Serotype B Strain PMB2707 (B44) (VR-MVR-10021, Version 3.0),
- Supplemental Dilutional Linearity Data for hSBA Validations for *Neisseria meningitidis* Serogroup B Strain PMB2001 (A56), PMB2707 (B44), PMB80 (A22) and PMB2948 (B24) (VR-VTR-10129, Version 1.0),
- Bridging of the Serum Bactericidal Assay Using Human Complement (hSBA) for *Neisseria meningitidis* Serogroup B Strains PMB2707 (B44) and PMB2948 (B24) to (b) (4) (VR-VTR-10753, Version 1.0),
- Bridging of the Serum Bactericidal Assay Using Human Complement (hSBA) for *Neisseria meningitidis* Serogroup B Strains PMB2001 (A56) and PMB80 (A22) to (b) (4) (VR-VTR-10766, Version 1.0),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup A (MenA) Strain F8238 (VR-MVR-10094, Version 1.0),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup C (MenC) Strain C-11 (VR-MVR-10092, Version 1.0),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup W (MenW) Strain MP01240070 (VR-MVR-10088, Version 1.0), and
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup Y (MenY) Strain S-1975 (VR-MVR-10091, Version 1.0).

The following document regarding clinical immunogenicity assays was submitted in Module 5.3.1.4 of BLA125770/0.7:

- Specificity of *Neisseria meningitidis* Serotype ACWY Serum Bactericidal Assay using Human Complement (VR-MVR-10457, Version 1.0).

The following documents regarding clinical immunogenicity assays were submitted in Module 5.3.1.4 of BLA125770/0.13:

- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup A (MenA) Strain F8238 (VR-MVR-10094, Version 2.0),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup C (MenC) Strain C-11 (VR-MVR-10092, Version 2.0),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup W (MenW) Strain MP01240070 (VR-MVR-10088, Version 2.0), and
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup Y (MenY) Strain S-1975 (VR-MVR-10091, Version 2.0).

The following document regarding clinical immunogenicity assays was submitted in Module 5.3.1.4 of BLA125770/0.16:

- Specificity of *Neisseria meningitidis* Serotype ACWY Serum Bactericidal Assay using Human Complement (VR-VTR-11133, Version 1.0).

All the reports relevant to hSBAs against *Neisseria meningitidis* serogroup B strains have been reviewed during the approval of BLA125549 for Trumenba®. The validations of hSBAs against *Neisseria meningitidis* serogroups A, C, W, and Y have not been reviewed previously by statistical reviewer and are covered in this review memo.

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

The following documents submitted to the BLA are reviewed and/or referenced:

- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup A (MenA) Strain F8238 (VR-MVR-10094, Version 1.0 dated October 25, 2021) (BLA125770/0.0, received October 21, 2022),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup C (MenC) Strain C-11 (VR-MVR-10092, Version 1.0 dated October 23, 2021) (BLA125770/0.0, received October 21, 2022),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup W (MenW) Strain MP01240070 (VR-MVR-10088, Version 1.0 dated October 23, 2021) (BLA125770/0.0, received October 21, 2022),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup Y (MenY) Strain S-1975 (VR-MVR-10091, Version 1.0 dated October 25, 2021) (BLA125770/0.0, received October 21, 2022).
- Specificity of *Neisseria meningitidis* Serogroup ACWY Serum Bactericidal Assay using Human Complement (VR-MVR-10457, Version 1.0 dated August 2, 2018) (BLA125770/0.7, received February 9, 2023),
- Response to 6 March 2023 FDA Information Request (IR) (BLA125770/0.11, received April 3, 2023),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup A (MenA) Strain F8238 (VR-MVR-10094, Version 2.0 dated March 29, 2023) (BLA125770/0.13, received April 28, 2023),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup C (MenC) Strain C-11 (VR-MVR-10092, Version 1.0 dated March 29, 2023) (BLA125770/0.13, received April 28, 2023),
- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup W (MenW) Strain MP01240070 (VR-MVR-10088, Version 1.0 dated March 29, 2023) (BLA125770/0.13, received April 28, 2023),

- Method Validation of the Serum Bactericidal Assay Using Human Complement (hSBA) Against *Neisseria meningitidis* Serogroup Y (MenY) Strain S-1975 (VR-MVR-10091, Version 1.0 dated March 29, 2023) (BLA125770/0.13, received April 28, 2023),
- Response to 10 April 2023 FDA IR (BLA125770/0.13, received April 28, 2023), and
- Specificity of *Neisseria meningitidis* Serogroup ACWY Serum Bactericidal Assay using Human Complement (VR-VTR-11133, Version 1.0 dated May 19, 2023) (BLA125770/0.16, received May 24, 2023).

The following document submitted to the IND is also referred to when reviewing validations of the hSBAs:

- Response to 18 August 2022 FDA IR (IND17319/147, Module 1.11.3, dated September 26, 2022, received September 27, 2022).

4. A COMBINED REVIEW OF THE METHOD VALIDATIONS OF THE HSBAS AGAINST MENA STRAIN F8238, MENC STRAIN C-11, MENW STRAIN MP01240070, AND MENY STRAIN S-1975

4.1 Introduction

Pfizer developed a pentavalent meningococcal vaccine (*Neisseria meningitidis* serogroups A, B, C, W, and Y vaccine [MenABCWY]) by combining Trumenba® (group B bivalent (b) (4) and Nimenrix® (meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine [MenACWY-TT]). As part of the immunogenicity objectives in clinical studies, the serum bactericidal activity using human complement of clinical samples needs to be determined against meningococcal serogroups A, C, W, and Y (MenACWY).

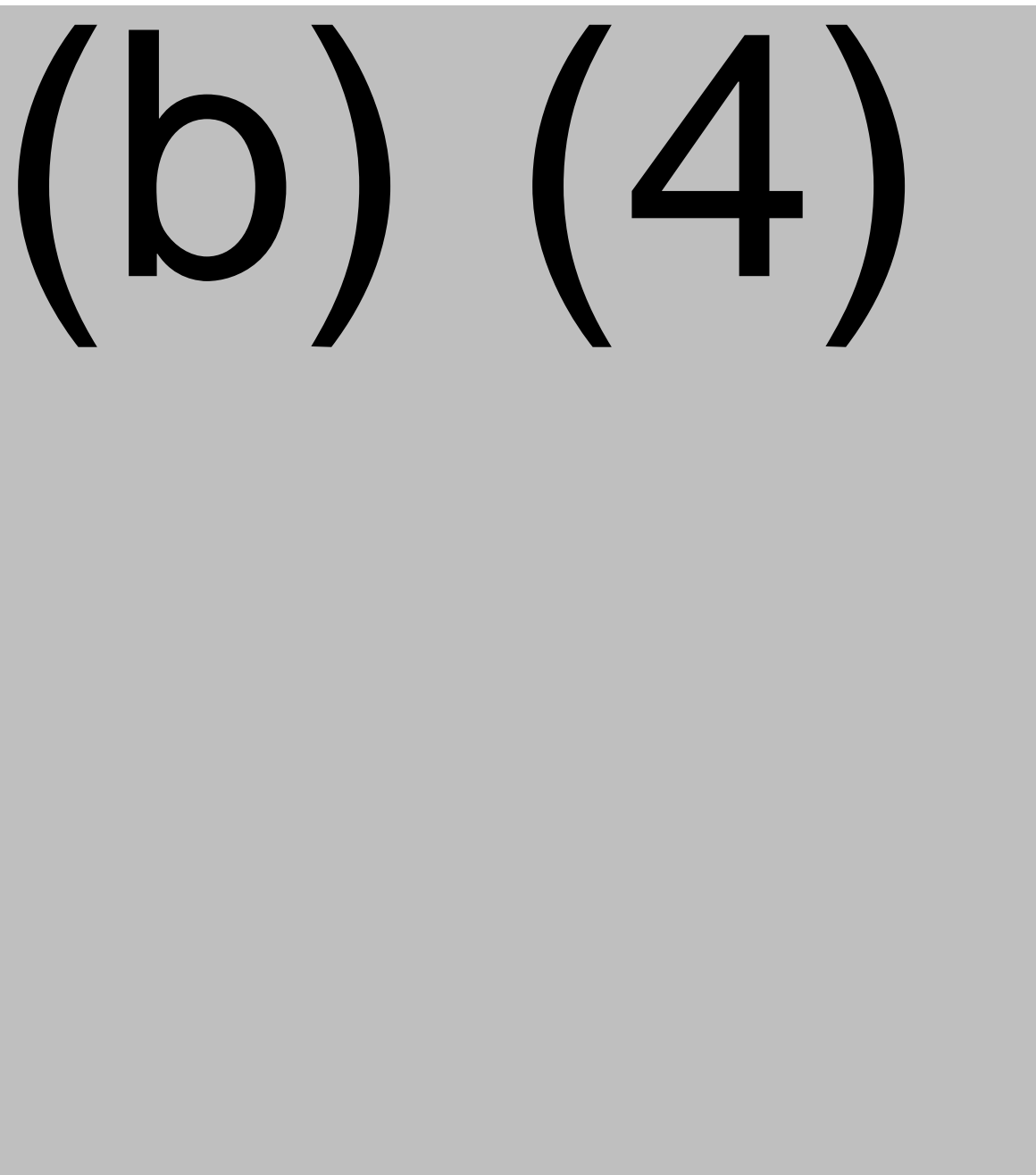
The hSBA for *Neisseria meningitidis* is designed to quantify functional antibodies in human serum samples that bind to bacteria and, in the presence of functional human complement, initiate the complement cascade that ultimately results in the formation of a membrane attack complex and destruction of the bacteria. An (b) (4)

The hSBA is the accepted surrogate of efficacy for meningococcal vaccines.

Original validation experiments were conducted in 2021 for hSBAs against MenA strain F8238 (expressing factor H binding protein [fHBP] variant B22), MenC strain C-11 (expressing fHBP variant A10), MenW strain MP01240070 (expressing fHBP variant A26), and MenY strain S-1975 (expressing fHBP variant A07), respectively, to assess relative accuracy/dilutional linearity, precision, LLOQ, ULOQ, and LOD. Per FDA request dated August 18, 2022, supplemental validation experiments were performed to confirm the linearity and precision assessment with additional samples for each serogroup. The final evaluation of linearity and precision included combined data from the original and supplemental validations.

Assay specificity was assessed and summarized in separate reports. Original specificity experiments were performed using (b) (4) serum samples with homologous and heterologous antigens to confirm assay specificity. In the original assessment, potential interference was only tested between MenA and MenW, and between MenC and MenY. Per FDA request dated January 10, 2023, supplemental specificity experiments were performed using (b) (4) serum samples to additionally assess specificity when all the MenACWY polysaccharides were used as heterologous competitors for each of the hSBAs.

4.2 Titer Determination



11 pages have been determined to be not releasable: (b)(4)

combined results from the original and supplemental specificity experiments are acceptable for the anti-MenACWY hSBAs.

5. CONCLUSIONS

This review memo focuses on the validations of the anti-MenACWY hSBAs to measure the bactericidal antibody against MenA strain F8238, MenC strain C-11, MenW strain MP01240070 and MenY strain S-1975.

The validation results showed acceptable accuracy and precision in the assay ranges. The LLOQ and ULOQ were determined to be (b) (4) and (b) (4) for anti-MenA and anti-MenC hSBAs and (b) (4) and (b) (4) for anti-MenW and anti-MenY hSBAs. The LOD was determined to be (b) (4) for anti-MenACWY hSBAs.

The specificity results are considered acceptable for the anti-MenACWY hSBAs.

In conclusion, I consider anti-MenACWY hSBAs adequate for their intended uses in support of this BLA.