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Review Completion Date / Stamped Date	
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Applicant	Pfizer
Established Name	Meningococcal Groups A, B, C, W, and Y Vaccine
(Proposed) Trade Name	PENBRAYA

Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	Suspension for injection following reconstitution of a single-dose vial of sterile lyophilized powder with the accompanying pre-filled syringe of sterile suspension
Dosage Form and Route of Administration	Intramuscular injection of 0.5mL/dose
Dosing Regimen	Two doses administered 6 (b) (4) months apart
Indication and Intended Population	Active immunization of individuals 10 through 25 years of age to prevent of invasive disease caused by Neisseria meningitidis serogroups A, B, C, W and Y

Table of Contents

Glossary	4
1. Executive Summary	4
2. Regulatory Background	5
3. Submission Quality	6
4. Significant Issues Related to Other Review Disciplines	6
4.1 Chemistry, Manufacturing, and Controls	6
5. Sources of Information Considered in the Review	6
5.1 Review Strategy	6
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review.....	7
6. Discussion of Individual Protocols, Studies, and Analyses	7
6.1 (b) (4) Validation for MenABCWY and MenACWY-TT.....	7
6.1.1 Study Design and Acceptance Criteria.....	7
6.1.2 Results	9
6.2 (b) (4) (b) (4) Validation	15
6.2.1 Study Design and Acceptance Criteria.....	15
6.2.2 Results	16
6.3 (b) (4) Potency Assay Validation Studies	16
6.3.1 (b) (4) Validation Study.....	17
6.3.2 (b) (4) Validation Study	18
6.3.3 Equivalence Assessment	19
6.3.4 Duplicate Immunogenicity Testing Justification.....	20
6.4 Equivalence of the (b) (4) Reference Materials	21
6.5. MenACWY-TT Assay Comparability Studies.....	22
6.5.1 Design and Analysis Methods	23
6.5.2 Results	23
7. Additional Statistical Issues	25
8. Conclusions.....	Error! Bookmark not defined.
8.1 Statistical Issues and Collective Evidence	25
8.2 Conclusions and Recommendations.....	25

GLOSSARY

%CV	percent coefficient of variation
BLA	biologics licensing application
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CMC	chemistry and manufacturing controls
DP	drug product
DS	drug substance
IR	information request
PPQ	process performance qualification
SD	standard deviation
SE	standard error
TI	tolerance interval
TOST	two one-sided tests
USP	United States Pharmacopeia

1. EXECUTIVE SUMMARY

In this original BLA, Pfizer seeks approval for their pentavalent meningococcal vaccine PENBRAYA for active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y. PENBRAYA is packaged as a single-dose vial of lyophilized MenACWY-TT drug product (DP) and a pre-filled syringe containing a single-dose of MenB. Before administration, MenACWY-TT is reconstituted with MenB to yield the pentavalent vaccine (MenABCWY). MenACWY-TT has been marketed by GlaxoSmithKline Biologicals (GSK) in the European Union as Nimenrix and was acquired by Pfizer in 2015. MenB is based on Trumenba, Pfizer's meningitis B vaccine that was approved in the US in 2014. MenB (b) (4) but the drug substance (DS) and DP assays are the same as those for Trumenba.

This review focuses on the (b) (4) assay validation for (b) (4) of the MenACWY-TT and (b) (4) of the MenABCWY, the (b) (4) (b) (4) for the MenB, and the (b) (4) potency for the MenB. This review also focuses on the comparability of the MenACWY-TT reference standards and the transfer studies for the MenACWY-TT assays as part of the transfer of manufacturing from GSK to Pfizer.

Based on communication with the product reviewer, I did not review the DS assay validation or CMC materials. Stability and shelf-life of the final MenABCWY vaccine is based on the stability of MenACWY-TT and MenB. No statistical analyses were conducted for stability of the two DPs; therefore, I did not review the stability or shelf-life information.

Pfizer submitted validation study results for (b) (4) for MenACWY-TT and MenABCWY and (b) (4) potency and (b) (4) for MenB. The validation of the MenB assays was acceptable, but the validation of (b) (4) did not adequately demonstrate that Pfizer's routine testing lab had acceptable accuracy, precision, and linearity over the assay's range because Pfizer neither assessed all validation parameters at their routine testing lab nor assessed all validation parameters at their original testing lab and demonstrated equivalence between the original and routine lab. A comment was sent to Pfizer requesting supplemental analyses to remedy these issues. While Pfizer's response did not fully address CBER's concerns, the data and my own analyses did demonstrate acceptable performance and the routine testing lab is considered acceptably validated for this assay.

For MenACWY-TT, Pfizer conducted transfer studies to demonstrate the equivalence of GSK and Pfizer's labs when performing the (b) (4) polysaccharide content, and (b) (4) assays. While Pfizer did not fully address CBER's concerns about their statistical methods not accounting for correlation induced by the transfer study design, the totality of data suggest that Pfizer has acceptable assay performance for these assays. Pfizer also established equivalence of the interim, primary, and working reference materials for MenACWY-TT and MenABCWY.

Overall, the statistical issues in the CMC validation studies and analyses were resolved during the BLA review, and Pfizer's labs have acceptable performance for the critical DP assays. Therefore, I recommend approval of this original BLA.

2. REGULATORY BACKGROUND

In this original BLA, Pfizer seeks licensure of their pentavalent meningococcal vaccine, PENBRAYA for immunization of individuals aged 10 to 25 years of age to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W-135, and Y. PENBRAYA consists of a single-dose vial of lyophilized MenACWY-TT and a single-dose syringe prefilled with the liquid MenB. The vaccine (MenABCWY) is administered after MenACWY-TT is reconstituted with MenB using the pre-filled syringe.

MenACWY-TT has been marketed outside of the U.S. as Nimenrix, which Pfizer acquired from GSK in 2015. Nimenrix was first approved in the European Union in 2012 and is currently marketed in 59 countries. MenB is based on Trumenba but has a (b) (4) (b) (4) to ensure correct dosing. Trumenba was approved under accelerated approval in the U.S. in 2014.

The MenABCWY vaccine is formulated with the A, B, C, W-135, and Y serogroup antigens at 5µg/dose and the MenB A and B subfamily antigens each at 60µg/dose.

Table 1 shows the CMC statistical information requests (IR) sent and the responses received. All responses were acceptable.

Table 1. BLA 125770/0 CMC Statistical Information Requests (IR) and Responses

Submission	Request Sent	Response Received	Summary
BLA 125770/0.19	04/06/2023	05/01/2023	Request to either remove Content Uniformity testing or propose a statistically reasonable procedure; Pfizer removed the Content Uniformity testing as requested.
BLA 125770/0.20	04/24/2023	05/05/2023	Request for more details about MenACWY-TT (b) (4) reference standard comparability study; Pfizer provided the additional details as requested.
BLA 125770/0.23	06/12/2023	06/26/2023	Request for additional analyses of CMC assay validation data using appropriate statistical methods to demonstrate equivalence between testing sites; Pfizer committed to provide the requested analyses in a subsequent submission. Request for additional information about Men B (b) (4) validation a (b) (4) and MenACWY-TT assay transfer studies; Pfizer provided the requested information about (b) (4)
BLA 125770/0.25	06/12/2023	07/27/2023	Pfizer provided the additional analyses requested in the 06/12/2023 IR for (b) (4) and additional information about the MenACWY-TT assay transfer studies;

Source: Created from BLA 125770/0

3. SUBMISSION QUALITY

The submission was adequately organized for conducting a complete CMC statistical review without unreasonable difficulty.

4. SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to product review for further details.

5. SOURCES OF INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on validation of the (b) (4) assay validation for (b) (4) (b) (4) of MenACWY-TT and (b) (4) of MenABCWY, the (b) (4) (b) (4) for MenB, and the (b) (4) potency for the MenB. This review also focuses on the comparability of the MenACWY-TT reference standards and the transfer studies for the MenACWY-TT assays as part of the transfer of manufacturing from GSK to Pfizer.

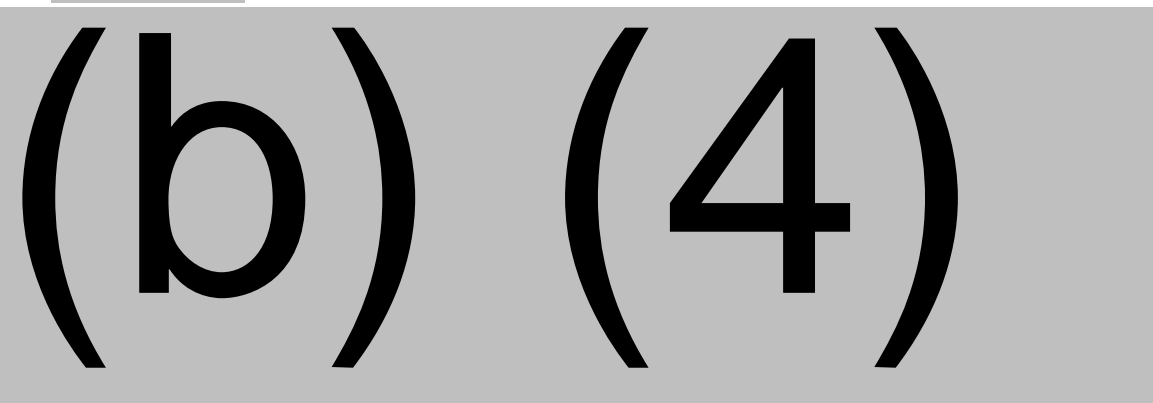
Based on communication with the product reviewer, I did not review the DS assay validation or other CMC materials. Stability and shelf-life of the final MenABCWY vaccine is based on the stability of MenACWY-TT and MenB. No statistical analyses were conducted for stability for the two DPs; therefore, I did not review of the stability or shelf-life information.

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

- BLA 125770/0.0 (seq. 0001):
 - Modules 3.2.P.5.3 for MenACWY-TT, MenB, and MenABCWY
- BLA 125770/0.10 (seq. 0012): Module 1.11.1
- BLA 125770/0.12 (seq. 0014): Module 1.11.1
- BLA 125770/0.14 (seq. 0019): Module 1.11.1
- BLA 125770/0.15 (seq. 0020): Module 1.11.1
- BLA 125770/0.23 (seq. 0031):
 - Module 1.11.1
 - Module 3.2.R
- BLA 125770/0.25 (seq. 0035): Module 1.11.1

6. DISCUSSION OF INDIVIDUAL PROTOCOLS, STUDIES, AND ANALYSES

6.1 (b) (4) Validation for MenABCWY and MenACWY-TT



6.1.1 Study Design and Acceptance Criteria



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

(b) (4)

6.3(b) (4) Potency Assay Validation Studies

The (b) (4) potency assay is used to measure the potency of the MenB bivalent DP component by measuring the immune response of mice after exposure to the MenB bivalent DP. (b) (4)

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

(b) (4)

Reviewer's Comment: *The accuracy results for MenB are reasonably close to 100%, although the confidence intervals are somewhat wide. However, given the desire to avoid unnecessary animal testing and the expected variability of these assays, these results are acceptable. The accuracy results for Trumenba suggest systematic bias downwards, however, these results are highly uncertain (extremely wide confidence intervals), based on an extremely small sample size, and not necessarily applicable to the MenB bivalent DP. Therefore, after discussion with the product reviewer, I am not concerned about the assay performance based on the Trumenba results.*

6.3.3 Equivalence Assessment

Pfizer analyzed the subfamily A and B reference standards (b) (4) results from (b) (4) and (b) (4) to demonstrate equivalency. A test of equal variances was performed to demonstrate homogeneity of variances for each subfamily. Because that test was not statistically significant, Pfizer concluded consistent variances. A (b) (4) of equal means was performed to demonstrate equivalency for both subfamilies, and because the differences in average (b) (4) values were not statistically significant, Pfizer concluded that the two labs are equivalent.

Reviewer's Comment: *Conclusion of homogenous variances or equivalent means based on a hypothesis test with a null hypothesis of no difference is not appropriate, as non-significant tests are inconclusive and with a small sample size, such tests may not detect meaningful differences in assay performance. Therefore, I do not present detailed results from these tests. An IR (12 June 2023) was sent to Pfizer about this issue. In their response, Pfizer agreed that the statistical methods were not appropriate to confirm*

*equivalency and provided the results of the typical (b) (4) for
equivalence using original scale data.*

(b) (4)

1 page has been determined to be not releasable: (b)(4)

6.5. MenACWY-TT Assay Comparability Studies

Until phase 3 clinical testing, MenACWY-TT was manufactured at GSK. For phase 3 clinical testing, manufacturing transferred to Pfizer (b) (4). As part of this transfer, the CMC assays were transferred. For the (b) (4) assays, except identity and (b) (4) and for the (b) (4) assay, Pfizer completed transfer studies that assessed the equivalence of the means at GSK and Pfizer.

In all the comparability studies, Pfizer used a (b) (4) with a 5% significance level (90% CI) to demonstrate comparability of the means at GSK and Pfizer. The equivalence acceptance intervals were set at (b) (4) for (b) (4) and the polysaccharide content assays and at (b) (4) for the (b) (4) assay, where s is the assay intermediate precision standard deviation estimated during the validation at GSK.

Reviewer's Comment: *Adequate validation of Pfizer's assays via demonstration of equivalence to GSK's assays assumes that GSK has adequately validated their lab for these assays. I briefly review the results of GSK's validation where Pfizer provided them in this submission.*

The use of (b) (4) is acceptable. In the original submission, Pfizer did not describe how the acceptance criteria for the equivalence tests were established. In Pfizer's response to an IR about this (BLA 125770/0.25), Pfizer provided a description of how the acceptance criteria were defined.

For (b) (4) and the (b) (4) assay, Pfizer used a (b) (4) design with multiple sources of correlation, including analyst, run, and instrument, but Pfizer's analysis does not account for any of these sources of correlation. Pfizer argues that because the multiple samples tested within each run were prepared independently, an assumption of independence is reasonable. However, even with independent preparations, assays can exhibit strong within-run correlation. For (b) (4) while not ideal, the assumption of independence is unlikely to substantially impact the results. For (b) (4) since the assay is a chemical assay and not a bioassay, we expect low within run correlation, so the assumption of independence is reasonable.

For the polysaccharide assays, Pfizer used a (b) (4) design at their lab to collect data and historical release data from GSK, which lacks replicates and may lack multiple observations from the same analyst, to establish equivalence. The substantial difference in study designs makes adjustment for correlation in data collection more difficult, but not impossible. However, while not ideal, the assumption of independence is unlikely to substantially impact the results.

6.5.1 (b) (4)

At each lab, (b) (4) MenACWY-TT lot was analyzed in (b) (4) by (b) (4) analysts with (b) (4) runs per (b) (4) for a total of (b) (4) results for each serogroup. Table 17 shows the results. All four serogroups met the pre-specified acceptance criteria for equivalence.

(b) (4)

Reviewer's Comment: Pfizer systematically produces slightly higher (b) (4) values than GSK, but the differences in means are small relative to the (b) (4) values and the confidence intervals are tight, suggesting equivalence between the two labs. Pfizer did not examine the comparability the variability at Pfizer compared to GSK. However, Pfizer present the repeatability and intermediate precision at GSK and precision results from both labs using the equivalence data. GSK's repeatability %RSD ranged from (b) (4) to (b) (4) by serogroup and IP %RSD ranged from (b) (4) by serogroup and lot. From the equivalence data, both labs have %RSD ranging from (b) (4) Overall, these results suggest that Pfizer and GSK are comparable, and that Pfizer has acceptable precision.

6.5.2 Polysaccharide Contents

The polysaccharide content of each of the four serogroups (A, C, W, Y) and the total polysaccharide content (C, W, and Y) are measured by several different assays, but Pfizer used a similar transfer study design for all five quality attributes.

For each quality attribute, Pfizer compared historical internal control data from GSK to newly collected data from an internal control lot assayed at Pfizer. Table 18 shows the specific design of each study.

Table 17. Polysaccharide Content Assays for MenACWY-TT: Comparability Study Design

Polysaccharide	GSK: Number of Observations	Pfizer: Study Design for New Data
A	(b) (4)	(b) (4)
C		
W		
Y		
Total		

Source: Module 3.2.P.5.3 Validation of Analytical Procedures – Analytical Transfer Summary Report, BLA 125770/0.0

Table 19 shows the results. All quality attributes met the pre-specified acceptance criteria for equivalence.

Table 18. Polysaccharide Content Assays for MenACWY-TT: Assay Comparability Results

Polysaccharide
A
C
W
Y
Total

(b) (4)

Source: Tables 3.2.P.5.3-15, 3.2.P.5.3-19, 3.2.P.5.3-23, 3.2.P.5.3-26, 3.2.P.5.3-26, Module 3.2.P.5.3 Validation of Analytical Procedures – Analytical Transfer Summary Report, BLA 125770/0.0

Reviewer's Comment: *The differences in means are small relative to the polysaccharide content values and the confidence intervals are tight, suggesting equivalence between the two labs. Ideally, Pfizer would have assessed comparability across the entire assay range.*

Pfizer presents the results from a full validation study at GSK that assessed accuracy, linearity, repeatability, and intermediate precision when testing validation standards. The results from this validation study demonstrated that these assays are accurate and precise over their ranges.

For serogroup A, Pfizer only examined the comparability of the precision by estimating the pooled standard deviation across both labs, which may mask differences in precision between labs. However, given that the %RSDs for GSK ranged from (b) (4) and that the pooled %RSDs were not substantially higher (b) (4) the precision at Pfizer is unlikely to be substantially higher than the precision at GSK. For serogroup C, Pfizer estimated the %RSD from the equivalence study at Pfizer as (b) (4) which is consistent with the %RSDs observed at GSK during validation (b) (4). For the rest of the serogroups and the total polysaccharides, Pfizer estimated the %RSD at each lab from the equivalence study and both labs had %RSDs (b) (4). These results suggest that the precision at Pfizer is comparable to GSK.

6.5.3 (b) (4)

At each lab, (b) (4) MenACWY-TT lot was tested by (b) (4) analysts in (b) (4) runs per analyst with (b) (4) independent replicates per run for a total of (b) (4) observations. Table 20 shows the results of the equivalence assessment.

Table 19. (b) (4) Assay for MenACWY-TT: Comparability Results

(b) (4)

Reviewer's Comment: *These results suggest that Pfizer and GSK are equivalent. No validation results from GSK or assessment of precision were provided. However, the (b) (4) is a (b) (4) assay that is expected to have extremely good precision at both labs and to be highly reproducible across labs. Therefore, this is acceptable.*

7. CONCLUSIONS

7.1 Statistical Issues and Collective Evidence

Pfizer submitted validation study results for their potency assays: (b) (4) for MenACWY-TT and MenABCWY and (b) (4) potency and (b) (4) (b) (4) for MenB. The validation for the MenB assays was acceptable, but the validation of (b) (4) did not adequately demonstrate that Pfizer's routine testing lab had acceptable accuracy, precision, and linearity over the assay's range because Pfizer neither assessed all validation parameters at their routine testing lab nor assessed all validation parameters at their original testing lab and demonstrated equivalence between the original and routine lab. A comment was sent to Pfizer requested supplemental analyses to remedy these issues. While Pfizer's response did not fully address CBER's concerns, my own analyses addressed CBER's concerns, and the routine testing lab is considered acceptably validated.

For MenACWY-TT, Pfizer conducted transfer studies to demonstrate the equivalence of GSK and Pfizer's labs when performing the (b) (4) polysaccharide content, and (b) (4) assays. While Pfizer did not fully address CBER's concerns about their statistical methods not accounting for the correlation induced by the transfer study design, the totality of data suggest that Pfizer has acceptable assay performance. Pfizer also established equivalence of the interim, primary, and working reference materials for MenACWY-TT and MenABCWY.

7.2 Conclusions and Recommendations

Overall, the statistical issues in the CMC validation studies and analyses were resolved during the BLA review, and Pfizer's labs have acceptable performance when performing the critical DP assays. Therefore, I recommend approval of this original BLA.