Application Type	Original BLA
STN	125701/0
CBER Received Date	April 26, 2019
PDUFA Goal Date	April 25, 2020
Division / Office	DVRPA /OVRR
Committee Chair	Joseph Temenak
Clinical Reviewer(s)	Anuja Rastogi
Project Manager	Michael J. Smith
Priority Review	No
Reviewer Name(s)	Charles (Yin Kiu) Cheung
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, Vaccine Evaluation Branch, Division of Biostatistics
Concurrence	Tsai-Lien Lin, Chief, Vaccine Evaluation Branch, Division of Biostatistics
Concurrence	John Scott, Director, Division of Biostatistics
Applicant	Sanofi Pasteur Inc.
Established Name	Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine
Trade Name	MenQuadfi
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Meningococcal Serogroup A, C, Y, and W polysaccharides (Monovalent conjugates), Tetanus Toxoid Protein (Carrier protein)
Dosage Form(s) and Route(s) of Administration	0.5 mL dose for intramuscular injection.
Dosing Regimen	- Individuals 2 years and older: a single dose. - Booster Vaccination: A single booster dose may be given to individuals at continued risk for meningococcal disease
Indication(s) and Intended Population(s)	For active primary and booster immunization for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y in individuals 2 years of age and older.

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1. Executive Summary

Sanofi Pasteur submitted a Biologics License Application for MenQuadfi Meningococcal Polysaccharide Tetanus Toxoid Conjugate Vaccine. The target indication for MenQuadfi is active primary and booster immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y in individuals 2 years of age and older. My review is divided into Chemistry and Manufacturing Control (CMC), and Clinical Bioassay sections.

In the CMC section, I reviewed the validation report of the (b) (4) test method used to measure total polysaccharide content of the Drug Product. In the validation study, all acceptance criteria were met and the analytical performance of the evaluated range appears to be acceptable. However, intermediate precision was evaluated at (b) (4) but not across the entire assay range. I defer to the product reviewer regarding the adequacy of the intermediate precision assessment and whether additional samples at different levels covering the entire assay range are needed.

In the clinical bioassay section, I reviewed the meningococcal antibody serum bactericidal assay using human complement (hSBA), which was used to assess immunogenicity of the antigens contained in the MenACYW conjugate vaccine. This assay was used in pivotal trials MET35, MET43, MET49, MET50, and MET56. In my exploratory analysis, the observed titers for serogroups C and W appear to be underestimated at the lower titer range ((b) (4)), whereas underestimation was not similarly observed at the higher titer range. This indicates a slope (b) (4) at the lower titer range for linearity, i.e. the observed titer is expected to increase more as the true titer increases. A consequence of this potential non-constant bias is that the true fold change of post-vaccination titer relative to pre-vaccination titer may be lower than the observed fold change. Thus, the seroresponse rates might have been overestimated. Nevertheless, in all clinical trials used to support the effectiveness of the vaccine (MET35, MET50, MET43, MET49, and MET56), the primary objectives were to establish non-inferiority of seroresponse in terms of the percent difference in seroresponse between MenQuadfi and an active comparator for the 4 serogroups. Because the potential bias in the estimation of seroresponse rate would affect both treatment groups in a similar way, and MenQuadfi appeared to elicit (oftentimes seemingly much) higher estimated seroresponse rates than the active comparator(s) in each study, the main conclusions of the studies are very unlikely to be affected. Therefore, I consider the hSBA to be acceptable for drawing the conclusions in the pivotal clinical studies submitted to this BLA.

2. Regulatory Background

2.1 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

(b) (4)

The test method was originally validated in 2014 (Reports Q_0521077 and Q_0520205) for MenQuad-TT A, C, Y, and W135. Since then, various changes were implemented to the analytical method for serogroups A, Y, and W135. Specifically, (b) (4) No changes were implemented to the method for serogroup C. Therefore, the applicant performed a re-validation study of the test method for serogroups A, Y, and W135 but not for serogroup C.

Serum Bactericidal Assay using Human Complement (hSBA)
The hSBA performed according to GDMS_559940 was validated in 2007. Per the request of CBER, the applicant performed supplemental studies that targeted the lower titer ranges of the assay for all serogroups. In 2016, the applicant performed a revalidation of GDMS_559940 and submitted a validation report to CBER via IND 14171/0.89 on June 6, 2016.

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

3.1 Review Strategy

In the CMC section, I reviewed the validation report of the re-validation study of the (b) (4) test method (Instruction Q_0279993) for serogroups A, W135, and Y, and the original validation report for serogroup C. In the clinical bioassay section, I reviewed the 2016 validation report of hSBA.

3.2 Submission Quality and Completeness

The documents that are relevant to my review appear to be complete. The applicant performed a revalidation of the hSBA (GDMS 559940) and submitted the validation report to IND 14171/0.89. The report was mentioned in this current BLA, but the report did not appear to have been submitted to the BLA.

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

The documents under review were:

1. BLA 125701/0 dated 4/26/2019
    - Module 2.5 *Clinical Overview*
    - Module 5.3.1.4 *Immunological Assay Methods*
    - Module 3.2.P.5.3 *Q-0521077 – Validation of Q_279993: Total & Free Polysaccharide Quantitation of TetraMen-T Conjugate Vaccine (Total Polysaccharide Only)*
    - Module 3.2.P.5.3 *Q-0635191 – Report for Protocol Q_0633361, Validation Extension of Q_0279993 Total & Free Polysaccharide Quantitation of MenQuad-TT Conjugate Vaccine to include* (b) (4)
2. IND 14171/0.89 dated 6/6/2016

- Module 5.3.1.4 *Q_0562648 – Validation Report for Instruction Q_0278737 "Serum Bactericidal Assay For Serogroups A, C, W-135 and Y Used for The Detection of Meningococcal Antibodies Using Human Complement"*

4. CHEMISTRY, MANUFACTURING, AND CONTROLS

4.1 Chemistry, Manufacturing, and Controls

I reviewed the test method for measuring the total polysaccharide content for serogroups A, C, W135, and Y.

(b) (4)

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(b) (4)

[redacted]

5. CLINICAL BIOASSAYS

5.1 Serum Bactericidal Assay using Human Complement (hSBA)

Functional meningococcal antibody activity against *Neisseria meningitidis* serogroups A, C, Y, and W was measured using the hSBA, performed by the Sanofi Pasteur Inc.'s Global Clinical Immunology (GCI) Department at Swiftwater, Pennsylvania (PA).

Principle: The hSBA is an *in vitro* method using a human complement source that measures the antibody-mediated, complement-dependent killing of bacteria. (b) (4)

[redacted]

Clinical studies MET35, MET44, MET50, MET43, MET49, and MET56 were submitted to the current BLA to support licensure of MenQuadfi for individuals 2 years of age and older. These studies were conducted between 2012 and 2017. In these studies, serogroup-specific efficacy was inferred from the proportion of subjects achieving a vaccine seroresponse measured by hSBA. Two different hSBA vaccine seroresponse definitions were used:

- In the 2 earliest studies (MET44 and MET50), hSBA vaccine seroresponse was defined as:
  - The response of subjects with an hSBA titer < 8 at baseline who then achieved an hSBA titer ≥ 8.
  - The response of subjects with an hSBA titer ≥ 8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer.
- In MET35, MET43, MET49, and MET56, hSBA vaccine seroresponse was defined as:
  - For a subject with a pre-vaccination titer < 8, the post-vaccination titer must be ≥16.
  - For a subject with a pre-vaccination titer ≥ 8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

Validation

I considered the 2016 revalidation report of the hSBA to be the most relevant validation report to review for the hSBA, because most clinical studies submitted to the BLA were completed in or after 2016.

Sanofi Pasteur revalidated the hSBA by assessing precision, repeatability, precision, accuracy, dilutional linearity, specificity, and lower limit of quantitation (LLOQ). The results were summarized in Table 2.

(b) (4)

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(b) (4)

(b) (4)

6. CONCLUSIONS

6.1 Statistical Issues and Collective Evidence

(b) (4) test method for measuring the total polysaccharide content:

- In the assessment of accuracy and repeatability, the evaluated range of (b) (4) is appropriate, because the range covers (b) (4) below the lower release specification and (b) (4) above the upper release specification. All acceptance criteria were met, and the analytical performance of the evaluated range appears to be acceptable. However, intermediate precision was only evaluated at the target level of (b) (4) but not at any other levels.

hSBA:

- Accuracy and precision of the assay passed the acceptance criteria in the common ranges evaluated (i.e., (b) (4) for serogroups A, C, and W135, and (b) (4) for serogroup Y. The ranges evaluated in the validation study appear to be reasonable.

- In the assessment of accuracy, the proportion of samples with observed median titers within (b) (4)-fold range of the expected titer was computed and tested against the acceptance criteria. The criterion of (b) (4)-fold difference between the observed median titers and expected titers appears to be loose, because the median of (b) (4) step titer results is a step titer value and checking whether the ratio is within (b) (4)-fold is not sufficiently sensitive to describe potential bias that is less than (b) (4)-fold. I plotted %relative bias against expected titers for each level of dilution for each sample. Descriptively, the observed titers for serogroups C and W appear to be underestimated at the lower titer range ((b) (4)), whereas underestimation was not similarly observed at the higher titer range. This indicates a slope (b) (4) at the lower titer range for linearity, i.e. the observed titer is expected to increase more as the true titer increases. A consequence of this potential non-constant bias is that the true fold change of post-vaccination titer relative to pre-vaccination titer may be lower than the observed fold change. Thus, the seroresponse rates might have been overestimated. Nevertheless, in all clinical trials used to support the effectiveness of the vaccine (MET35, MET50, MET43, MET49, and MET56), the primary objectives were to establish non-inferiority of seroresponse in terms of the percent difference in seroresponse between MenQuadfi and an active comparator for the 4 serogroups. Because potential bias in the estimation of seroresponse rate would affect both treatment groups in a similar way, and MenQuadfi appeared to elicit (oftentimes seemingly much) higher estimated seroresponse rates than the active comparator(s) in each study, the main conclusions of the studies are very unlikely to be affected.

6.2 Conclusions and Recommendations

For the (b) (4) test method for measuring the total polysaccharide content, I defer to the product reviewer regarding the adequacy of the intermediate precision assessment and whether additional samples at different levels covering the entire assay range are needed. The hSBA appears to be acceptable for drawing the conclusions in the pivotal clinical studies submitted to this BLA.