Summary Basis for Regulatory Action

Date: April 22, 2020

From: Joseph Temenak, Ph.D., Chair of the Review Committee

BLA STN#: 125701.0

Applicant Name: Sanofi Pasteur Inc.

Original Submission Date: April 26, 2019

Goal Date: April 24, 2020

Proprietary Name / Established Name: MenQuadfi / Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

Indication: Active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y for use in individuals 2 years and older.

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority:
Marion F. Gruber, Ph.D., Director, Office of Vaccines Research and Review

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA.

Document title	**Reviewer name - document date**
CMC Reviews • *CMC* • *Inspection waiver memo* • *Facilities review*	 Marcos Battistel, Ph.D. (CMC, OVRR/DBPAP) – April 15, 2020 Kathryn Matthias, Ph.D. (Meningococcal assays, OVRR/DBPAP) – April 15, 2020 Eric Peng, Ph.D. (Tdap assays, OVRR/DBPAP) – April 15, 2020 Xiao Wang, Ph.D. (HPV assays, OVRR/DVP) – April 16, 2020 Gregory Price, Ph.D. (OCBQ/DMPQ) – July 10, 2019 Gregory Price, Ph.D. (OCBQ/DMPQ) – April 8, 2020
Clinical Reviews • *Clinical* • *Postmarketing safety epidemiological review* • *BIMO*	 Anuja Rastogi, M.D., M.H.S. (OVRR/DVRPA) – April 22, 2020 Bethany Baer, M.D. (OBE/DE) – April 8, 2020 Malcolm Nasirah, Pharm.D., M.S. (OCBQ/DIS) – March 18, 2020
Statistical Reviews • *Clinical data* • *Non-clinical data*	 Elizabeth Teeple, Ph.D. (OBE/DB) – March 27, 2020 Yin Cheung, Ph.D. (OBE/DB) – October 29, 2019
Pharmacology/Toxicology Reviews • *Toxicology-Developmental toxicology*	 Joe Sun, Ph.D. OVRR/DVRPA – January 15, 2020
Labeling Reviews • *APLB* • *Other*	 Michael Brony, Pharm.D. (PNR Memo, OCBQ/APLB) – June 3, 2019; Michael Brony, Pharm.D. (Labeling review, OCBQ/APLB) – January 13, 2020 Daphne Stewart (Labeling review, OVRR/DVRPA) – April 15, 2020 Ramachandra Naik, Ph.D. (Labeling review, OVRR/DVRPA) – April 22, 2020
Other Reviews • *Analytical methods and product testing* • *Other*	 In-Support Testing: OCBQ/DBSQC – Salil Ghosh, Ph.D. – March 9, 2020 Analytical methods: OCBQ/DBSQC – March 20, 2020 – Anil Choudhary, Ph.D., MBA; Hsiaoling Wang, Ph.D./Tao Pan, Ph.D.; Hyesuk Kong, Ph.D. – April 7, 2020 Lot Release Protocol and Testing Plan Development: OCBQ/DBSQC – Marie Anderson, M.S., Ph.D. – April 17, 2020 Michael Smith, Ph.D. (Admin review, OVRR/DVRPA) – April 22, 2020

1. INTRODUCTION

On April 26, 2019, Sanofi Pasteur Inc. (henceforth referred to as Sanofi), Swiftwater, Pennsylvania (US License 1725) submitted a biologics license application (BLA) for a vaccine with the proposed proper name of Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine and the proposed proprietary name of MenQuadfi. MenQuadfi was proposed for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y for use in individuals 2 years of age and older. The vaccine dose is 0.5 mL and is supplied as a sterile solution for intramuscular injection in 2.0 mL single-dose vials. The single-dose vial (NDC 49281-590-58) is supplied in packages of 5 vials (NDC 49281-590-05).

2. BACKGROUND

MenQuadfi is a vaccine that contains active ingredients comprised of serogroup-specific polysaccharide antigens purified from *N. meningitidis* serogroups A, C, W, Y, separately conjugated to tetanus toxoid. Each 0.5 mL single dose of MenQuadfi is formulated to contain 10 µg of each polysaccharide antigen (A, C, W, Y) conjugated to a total of approximately 55 µg of tetanus toxoid (quantity depends on the (b) (4)).

Currently, two other quadrivalent meningococcal conjugate vaccines are licensed in the United States (US) for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. GlaxoSmithKline (GSK) produces Menveo (Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine) for use in individuals 2 months through 55 years of age; primary immunization is approved for individuals 2 months through 55 years of age, and a single booster dose is approved for individuals 15 through 55 years of age. Sanofi produces Menactra (Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine) for use in individuals 9 months through 55 years of age; primary immunization is approved for individuals 9 months through 55 years of age, and a single booster dose is approved for use in individuals 15 through 55 years of age. Sanofi is seeking an indication for MenQuadfi for use in individuals 2 years of age and older, with administration as primary immunization across this age range and booster immunization for 15 years of age and older.

3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

General Manufacturing Summary

MenQuadfi is a vaccine that contains *N. meningitidis* serogroup A capsular polysaccharide (MenA), *N. meningitidis* serogroup C capsular polysaccharide (MenC), *N. meningitidis* serogroup W capsular polysaccharide (MenW), and *N. meningitidis* serogroup Y capsular polysaccharide (MenY), each covalently bound to tetanus toxoid (TT), and is maintained in liquid form in an acetate buffer. The manufacture and formulation of MenQuadfi is performed at the Sanofi site in Swiftwater, PA. The filling,

release and stability testing of MenQuadfi as well as the final labeling and packaging (into cartons containing 5 vials of vaccine) are performed at the Sanofi site in Swiftwater, PA. *In vivo* stability testing of DP batches is performed at the Sanofi Pasteur (b) (4) facility in (b) (4) .

Some of the starting materials and drug substance intermediates used to manufacture MenQuadfi are also components of other licensed vaccines. *N. meningitidis* seed banks and polysaccharide purified bulk (b) (4) (Serogroups A, C, W, Y) were used in some of (b) (4) These drug substance intermediates are used to create new drug substances, *N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrates (Serogroups A, C, W, Y), that are further manufactured into the drug product.

Drug Substances (DSs)

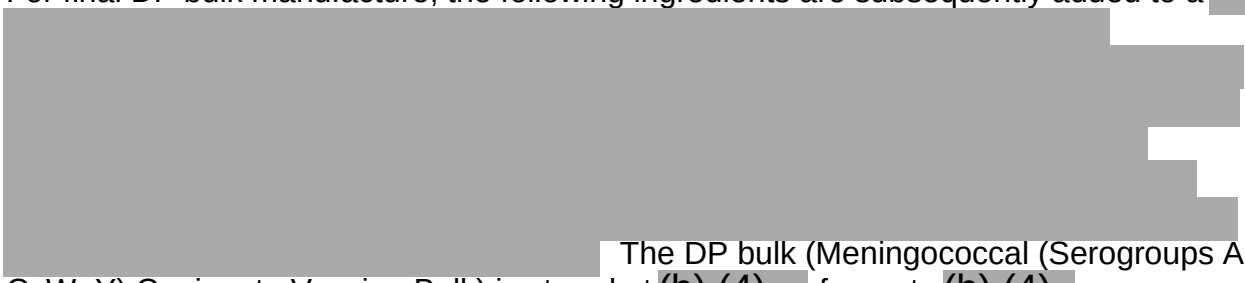
MenQuadfi vaccine is composed of four drug substances (MenA-TT, MenC-TT, MenW-, MenY-TT). These drug substances consist of the *N. meningitidis* serogroup A, C, W, Y capsular polysaccharides, respectively, covalently bound to tetanus toxoid. For the bulk TT, the starting material is a *Clostridium tetani* seed lot. The manufacture of the Drug Substances, *N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrates Serogroups A, C, Y, and W, consists of the following major manufacturing process stages:

(b) (4)

(b) (4)

Drug Product (DP)

For final DP bulk manufacture, the following ingredients are subsequently added to a (b) (4)



The DP bulk (Meningococcal (Serogroups A, C, W, Y) Conjugate Vaccine Bulk) is stored at (b) (4) for up to (b) (4) .

Table 1: Composition of the Final Container Drug Product - Meningococcal (Serogroups A, C, Y, W) Conjugate Vaccine

Component	Formulated Quantity (0.5 mL Dose)	Function
Meningococcal (Serogroup A) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Meningococcal (Serogroup C) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Meningococcal (Serogroup W) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Meningococcal (Serogroup Y) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Tetanus Toxoid, Filtered Concentrate	55 µg*	Carrier Protein
Sodium Chloride (within (b) (4) Sodium Chloride Solution)	3.35 mg (0.67%)	Excipient used to (b) (4)
Sodium Acetate (within (b) (4) Sodium Acetate, (b) (4) Solution)	1.23 mg (30mM)	Excipient used to (b) (4)

* Tetanus toxoid quantity is approximate and dependent on the (b) (4) for the conjugates used in each formulation.

Filling

The filling of the unit dose vials begins with transporting the Meningococcal (Serogroups A, C, W, Y) Conjugate Vaccine Bulk in a (b) (4) During the filling operation, the volume accuracy is routinely checked by (b) (4) the liquid content of the vials during the run ((b) (4)). Latex free stoppers are placed into vials, and 13 mm caps are placed on stoppered vials. Samples of unlabeled vials are taken out for release testing and all samples are 100% manually inspected prior to delivery to analytical lab for testing. The date of manufacture of MenQuadfi is defined as the date of final fill of the formulated drug product.

After inspection, the MenQuadfi unit dose vials are removed from storage, transported to the packaging area, labeled and packaged in Building (b) (4). The packaged Drug Product

is placed in cold storage at 2 ºC to 8 ºC until it is transported to US distribution centers using a validated carrier. Temperature monitoring devices accompany every shipment.

Cartons/Containers
MenQuadfi is pre-filled into 2 mL borosilicate clear glass vial, each containing a 0.5 mL single dose. The physical appearance of the DP in the final unit dose vial is a clear solution. The vials are labeled and packaged into a carton that contains 5 vials. Final cartons of MenQuadfi are stored at 2 to 8°C until release and shipment for distribution.

Analytical Procedures
The analytical methods and their validations and/or qualifications reviewed for the MenQuadfi drug substance and drug product were found to be adequate for their intended use. With the exception of the (b) (4) assay that was performed and validated by (b) (4), all the other methods are performed and validated at the Sanofi Swiftwater site.

Three DP consistency/process validation bulk lots were manufactured in Building (b) (4)

In addition to Bulk lots, three DP consistency/process validation unit dose vial lots were filled in (b) (4) at Sanofi's Swiftwater, PA facility using 2 mL borosilicate glass vials with a 13 mm stopper and 13 mm flip cap. The consistency/process validation unit dose vial lots utilized bulk lots manufactured with (b) (4) DS material and were sterile filtered into (b) (4). (b) (4) filled on Line (b) (4) utilizing bulk material manufactured with DS produced in (b) (4) and was sterile filtered into a (b) (4). All batches were filled following the processing parameters. The consistency/process validation lots were assessed against acceptance criteria, which consisted of in-process controls and critical quality attributes (CQAs). The supplemental GMP lot was assessed against the CQAs to ensure all release acceptance criteria were met. All (final and in-process) acceptance criteria were met.

Release Testing
The analytical methods and their validations and/or qualifications for the MenQuadfi vaccine DP were found to be adequate for their intended use. Table 2 below shows the tests and release specifications for MenQuadfi (b) (4) Final Filled Product.

Table 2: Release Specifications for MenQuadfi (b) (4) Final Drug Product

Test	Specifications
(b) (4) – Final Bulk ((b) (4))	(b) (4)
Total Polysaccharide, by serogroup ((b) (4))	(b) (4) for each group (A,C,Y,W)
(b) (4) Free Polysaccharide (b) (4)	(b) (4) for each group (A,C,Y,W)
Total Protein ((b) (4))	(b) (4)
Sterility – Filled Container ((b) (4))	No Growth
(b) (4)	(b) (4)
Volume Check ((b) (4))	No Less Than 0.5 mL
Abnormal Toxicity ((b) (4))	(b) (4) ***
Endotoxin by (b) (4)	(b) (4)
Visual examination	Major defects AQL (b) (4); Minor defects AQL (b) (4); Critical Defects: (b) (4)
Visual exam and (b) (4) test	Rejects – (b) (4) Rejects – (b) (4)
(b) (4)	(b) (4)
Identity - Labeled final container ((b) (4))	Identifies as serogroups A, C, Y, W polysaccharide; (b) (4)

(b) (4)

Stability of the Final Bulk Product and DP and Proposed Shelf-life

Sanofi submitted information for stability studies to be performed on (b) (4) MenQuadfi Final Bulk Product lots ((b) (4)) and (b) (4) DP lots in unit dose vials ((b) (4) clinical lots: (b) (4) and (b) (4)). Routine/real-time stability studies for the final bulk material is performed at (b) (4) , with time points/data available for (b) (4) . Real-time stability studies for the Final DP/unit dose vials are being performed for both routine (2ºC to 8ºC) and accelerated conditions studies (b) (4) . For the routine/real-time studies, the samples will be tested at time points 0, 1, 3, 6, 9, 12, 18, 24, 30, 36, (b) (4) while stored at 2°C to 8°C. Sanofi also conducted (b) (4) studies to assess the stability of the Drug Product (unit dose vials) after (b) (4) . The study included 2 mL unlabeled vials (lot (b) (4)) with (b) (4) , vials in their secondary packaging (i.e., carton) to represent the marketing presentation, and control

samples ((b) (4)) stored at the same temperature that were not (b) (4) .

The real-time stability studies (2°C to 8°C) for the DP, unit dose vials, and for (b) (4) Drug Product lots ((b) (4)) are on-going. Results are available through (b) (4) at 2°C to 8°C for the clinical lots (b) (4) , and through 18 months for the (b) (4) . All data to-date have met the acceptance criteria. The accelerated stability studies ((b) (4)) for all (b) (4) lots of the DP, unit dose vials, ((b) (4)) are completed through 6 months. Test results from the (b) (4) study for both the immediate (unlabeled) and marketing packaging successfully met the acceptance criteria for all stability indicating quality attributes, with no discernable difference between the controlled and (b) (4) sample groups. The real-time stability studies ((b) (4)) for the DP,(b) (4) Phase III clinical consistency/process validation lots ((b) (4)) and supplemental (b) (4) are completed. All data met the acceptance criteria through 6 months of storage at (b) (4) .

Results from the studies described above support the stability of MenQuadfi Vaccine Finished Product in a 2 mL United States Pharmacopoeia (USP) Type I borosilicate clear glass vial with a 13 mm opening and a 13 mm gray butyl rubber (Latex Free) serum stopper. However, real-time stability data trend analysis showed that the level of free (unconjugated) *N. meningitidis* serogroup A polysaccharide (MenA), a critical quality attribute, increases at a rate of (b) (4) . The worst-case scenario rate of increase in free MenA translates into a (b) (4) increase over a 36-month storage period. Since the release and stability specification for free MenA are (b) (4) , respectively, a DP batch released at the release specification limit may not conform to the stability specification beyond 36 months of storage. Therefore, the expiry dating period of MenQuadfi (in unit dose vials) was set to 36 months from the date of manufacture when stored at 2°C to 8°C.

Sanofi commits to placing at least (b) (4) of Unit Dose Vial Drug Product (if manufactured) on the (b) (4) stability program to assess quality of the product throughout the expiry in accordance with site procedure.

Adventitious Agents Safety Evaluation for Non-Viral Adventitious Agents: Information related to the materials of biological origin, criteria applied for selection of materials of biological origin, seed bank history testing and characterization data, raw material sources, purification/inactivation procedures applied during the manufacture of drug substance intermediates, DS and DP provide reasonable confidence that there is negligible risk of any possible viral contamination in the DP.

Exemption from the Abnormal Toxicity/General Safety Test (GST): In the cross-referenced IND submission of December 6, 2016, Sanofi requested an exemption for the Abnormal Toxicity /GST according to the Federal Register Volume 68, Number 42 (04

March 2003) and the final ruling in the Code of Federal Regulations (CFR) Title 21 Part 610.11 paragraph (g)(2). Since the results for the Phase I, II, Phase IIb/III GMP, Phase III clinical consistency/process validation and representative commercial lots were all within the established specification, CBER agreed with the removal of the test as a release test on the DP for all future lots.

Extractables and Leachables:
Compatibility between the DP with the Container Closure System was evaluated through Extractable/Leachable, Cytotoxicity and Stability studies.

Leachables from the Container Closure System into the DP were assessed by storing DP in (b) (4) 2 mL serum tubing vials with 13 mm stoppers and flip-off seal under normal conditions at 2°C to 8°C for (b) (4) as well as accelerated conditions of (b) (4) as compared to control samples stored in glass vials and compared to DP stored in same Container Closure System but in (b) (4) position. Sanofi provided 24 out of (b) (4) months for the ongoing long-term leachable study.

Extractables from the Container Closure system into the Drug Product were assessed by subjecting the stopper to (b) (4) extraction with (b) (4) . Samples were subsequently analyzed for potential compounds that could be extracted from the stopper by the Drug Product solution. The data supports compatibility with the container closure system for up to 24 months of storage under normal conditions (2°C to 8°C).

a) CBER Lot Release
The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A testing plan was developed by CBER and will be used for routine lot release.

b) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of MenQuadfi are listed in the table below. The activities performed and inspectional histories are noted in Table 3.

Table 3: Manufacturing Facilities for MenQuadfi - Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification /Results
Drug substance and product manufacturing, final bulk product formulation, filling and packaging, quality control, release and stability testing. Sanofi Pasteur, Inc. 1 Discovery Drive Swiftwater, PA 18370	2518760	086723285	Waiver	Team Biologics June 6-15, 2018 VAI
Bulk Drug Substance manufacture (Tetanus Toxoid), quality control, release and stability testing. Sanofi Pasteur (b) (4)	(b) (4)	(b) (4)	Waived	Team Biologics (b) (4) VAI

Team Biologics conducted a surveillance inspection of the Sanofi Swiftwater, PA facility in June 2018. A Form FDA 483 was issued at the end of the inspection and all inspectional issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

Team Biologics performed a surveillance inspection of the Sanofi (b) (4) manufacturing facility in (b) (4). A Form FDA 483 was issued at the end of the inspection and all inspectional issues were resolved, and the inspection was classified as VAI.

Container/Closure System

The drug product is filled in 2 mL, United States Pharmacopoeia (USP) Type I borosilicate clear glass vials ((b) (4)) with a 13 mm butyl, latex free, stopper and a flip off seal ((b) (4)). Sanofi's Swiftwater, PA site performed the container closure integrity testing employing the (b) (4) container closure integrity test method; all acceptance criteria were met.

c) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

For the nonclinical safety evaluation of Meningococcal (Groups A, C, Y, W) Conjugate Vaccine, a repeat-dose toxicity study in rats was conducted to evaluate its systemic and local toxicity and to support its use in human clinical trials. A developmental toxicity (DART) study was conducted in rabbits to evaluate the risk of vaccination in women of childbearing potential.

Rats and rabbits were selected for the repeat-dose toxicity study and the DART study, respectively, as they are established models for these toxicity assessments of vaccines and they elicit an immune response to group A, C, W, and Y meningococcal polysaccharides following intramuscular injections of Meningococcal (Groups A, C, Y, W) Conjugate Vaccine. One human dose of MenACYW conjugate vaccine given to rats on four occasions by the IM route was well tolerated with no systemic or local signs of toxicity observed. The DART study showed no adverse effects on mating performance or fertility. There was no indication of maternal systemic toxicity induced during the gestation and lactation periods, no effect on pre- and post-natal development, and no indication of a teratogenic potential.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program for MenQuadfi vaccine. No studies were performed on special populations.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The applicant submitted data from eight clinical studies in support of this BLA, including five trials (one Phase 2 - MET50, and four Phase 3 - MET43, MET35, MET49, MET56) which were conducted at 232 sites in the US, including Puerto Rico. These 5 studies provided the pivotal immunogenicity and safety data to support the intended indication in children 2 years through 9 years, adolescent 10 years through 17 years, adults 18 years through 55 years, and older adults ≥56 years of age, and included data to support clinical lot consistency. A Phase 2 US study (MET44) was also included that provided additional safety and immunogenicity data in older adults ≥56 years of age. In addition, two early phase non-US studies (MET28 and MET32) were included that evaluated different vaccine formulations that varied based on the (b) (4) . Data generated from these two studies helped determine the final MenQuadfi formulation.

Table 4: Pivotal/Supportive Phase 3 study protocols for MenQuadfi vaccine

Study Number	Country	Description (relevance to US licensure)	Participant Ages	Study Groups: # Enrolled (#Exposed)
MET43	US	Phase 3 Controlled, DB, Multicenter, Immunogenicity/Safety, Lot-to-Lot Consistency, Primary Dose, Vaccine-naïve Adolescents/Adults, Noninferiority to Menactra	10 to <18 years 18 to 55 years	MenQuadfi Lot 1: 902 (895) MenQuadfi Lot 2: 895 (886) MenQuadfi Lot 3: 906 (900) Menactra: 641 (636)
MET35	US[#]	Phase 3 Controlled, DB, Multicenter, Immunogenicity/Safety, Primary Dose, Vaccine-naïve Children, Noninferiority to Menveo	2 to <6 years 6 to <10 years	MenQuadfi: 499 (497) Menveo: 501 (495)
MET49	US[#]	Phase 3 Controlled, DB, Multicenter Immunogenicity/Safety, Primary Dose, Vaccine-naïve Adults, Noninferiority to Menomune	56 to <65 years 65 to <75 years ≥75 years	MenQuadfi: 451 (448) Menomune: 455 (453)
MET56	US[#]	Phase 3 Controlled, DB, Immunogenicity/Safety, Multicenter, Booster Dose, History of Primary MCV4 (4y to 10y prior), Noninferiority to Menactra	≥15 years	MenQuadfi: 403 (402) Menactra: 407 (407)
MET50	US	Phase 2 Controlled, DB, Immunogenicity/Safety, Multicenter, Primary Dose, Noninferiority to Menveo. Concomitant Tdap + HPV4	10 to <18 years	MenQuadfi: 505 (499) Menveo: 507 (504) MenQuadfi+Tdap+HPV: 403 (377*) Tdap+HPV: 300 (273*)

Study Number	Country	Description (relevance to US licensure)	Participant Ages	Study Groups: # Enrolled (#Exposed)
MET44	US	Phase 2, Open-label, Controlled, Immunogenicity/Safety, Multicenter Primary dose, Vaccine-naïve Adults ≥56 years Comparator: Menomune	56 to 64 years ≥65 years	MenQuadfi 56-64y: 101 (101) MenQuadfi ≥65y: 100 (100) Menomune 56-64y: 50 (50) Menomune ≥65y: 50 (50)
MET28	Canada	Phase 1, Single-blind, Partially-controlled, Safety/Imm, Formulation Selection (b) (4)), Multicenter, Step-down (Adults, Toddlers, Infants) Infant controlled only-Menjugate	18 to 39 years 12 to 18 months 2 months	Adults Grp 1-(b) (4): 15 (15) Adults Grp 2-(b) (4): 15 (15) Toddler Grp 3-(b) (4): 21 (21) Toddler Grp 4-(b) (4): 20 (19) Infant Grp 5-(b) (4): 45 (46) Infant Grp 6-(b) (4): 45 (44) Infant Grp 7-(b) (4): 45 (43) Infant Grp 8- Menjugate: 44(44)
MET32	Australia	Phase 1/Phase 2, Controlled, Observer Blind, Multicenter Antigenic Dose and Protein Conjugate Selection Comparator: Neis-Vac-C	12 months	5 different dose groups: 310 (306) Neis-Vac-C group: 63 (62)

Source: STN 125701, Section 5.2-Tabular Listing of all Clinical Studies, adapted from Table 1. DB: double- blind, Adol.: adolescents, MCV4: meningococcal conjugate ACWY vaccine.
#: Includes sites in Puerto Rico. *exposure to all study vaccine doses, (b) (4) .
Menjugate (Meningococcal serogroup C CRM197conjugate vaccine, GSK) not licensed in US
NeisVax-C (Meningococcal serogroup C tetanus toxoid conjugate vaccine, Baxter International) not licensed in US

Immunogenicity Analyses:

Serum bactericidal anti-capsular antibodies have been associated with protection from invasive meningococcal disease due to serogroups A, C, W, Y. Serum bactericidal activity (antibodies) measured in assays using human complement (hSBA) as basis for inferring effectiveness of meningococcal conjugate vaccines was discussed and endorsed by a VRBPAC convened in April 2011. Immunologic non-inferiority to US-licensed vaccines based on hSBA seroresponse rates has been used to establish effectiveness of other meningococcal conjugate vaccines. During MenQuadfi clinical development, CBER advised the applicant (Type C Meeting, April 2016) that the Phase 3 primary immunogenicity (inferred effectiveness) objectives incorporate a 4-fold response[1] from baseline in the definition of seroresponse. This seroresponse definition

[1] Based on assay validation information that supported Lower Limit of Quantitation (LLOQ) 1:4.

was based on the increasing recognition of pre-existing titers at baseline in adolescents and adults. The applicant agreed with CBER's request and included the 4-fold vaccine hSBA seroresponse definition in all studies included in the Phase 3 program.

For the 5 main studies (MET35, MET43, MET49, MET50, and MET56) included in this application, hSBA immunogenicity endpoints were used to infer effectiveness of MenQuadfi in participants 2 years of age and older who received a primary vaccination dose and in participants 15 years of age and older who received a booster vaccination dose at least 4 years following a previous dose of a meningococcal (Groups A, C, W, Y) conjugate vaccine. The primary endpoint assessed the proportion of participants who achieved serogroup specific seroresponse 30 days post-vaccination compared to baseline (pre-vaccination). Seroresponse was defined as post-vaccination titer ≥ 1:16 for participants with pre-vaccination hSBA titer < 1:8, or post-vaccination titer at least 4-fold greater than the pre-vaccination titer for participants with pre-vaccination titer ≥1:8.

For each primary objective, non-inferiority of hSBA serogroup-specific hSBA seroresponse rates was evaluated at Day 30 after MenQuadfi vaccination compared to the corresponding responses at Day 30 after vaccination with a US-licensed MenACWY vaccine (active comparator). Non-inferiority was demonstrated if the lower limit of the 95% CI of the difference in seroresponse rates (MenQuadfi- comparator) was > -10%. The non-inferiority criteria were met for all serogroups across the main studies evaluating a primary dose or booster dose vaccination. By serogroup, the lower limit of the 95% CI of the difference in seroresponse rates across these studies were as follows:

- serogroup A: 0.74% to 14.8%
- serogroup C: 2.16% to 42.2%
- serogroup Y: -0.91% to 24.6%
- serogroup W: 4.3% to 22.5%

Secondary immunogenicity objectives evaluating serogroup-specific Geometric Mean Titers (GMTs) 30 days post-vaccination supported the findings of the primary analyses. Overall, the immunogenicity data based on hSBA endpoints were sufficient to demonstrate effectiveness of MenQuadfi primary and booster vaccination to support licensure.

Booster Dose Vaccination

Study MET56 evaluated the immunogenicity and safety of a single booster dose of MenQuadfi when compared to a single booster dose of Menactra in individuals 15 years of age and older who had received a meningococcal A, C, Y, W conjugate vaccine 4 to 10 years earlier. The safety and immunogenicity data from this study support the use of MenQuadfi as a booster dose vaccination in individuals 15 years of age and older.

Serology

Immunological assays were utilized in the clinical studies to determine non-inferiority of MenQuadfi to licensed meningococcal vaccines and to test for serological responses to non-meningococcal-specific vaccines administered concomitantly with MenQuadfi. The standard assay used to measure MenA, MenC, MenW, and MenY responses to

meningococcal vaccines was the hSBA. Additional assays included the Diphtheria Toxin Neutralization Assay (TNA (b) (4)), the Tetanus (b) (4) ELISA, four Pertussis (b) (4) ELISAs to measure responses to the Tdap (Adacel) vaccine, and the HPV-4 cLIA (b) (4) assay used to measure antibodies to HPV virus-like particle (VLP) types 6, 11, 16, and 18 (Gardasil).

Concomitant Vaccination

Safety and effectiveness of MenQuadfi when administered concomitantly with Tdap vaccine (Adacel) and HPV Quadrivalent (Types 6, 11, 16, & 18) vaccine (Gardasil) in adolescents 10 years through 17 years of age were evaluated in Study MET50. No evidence of interference in hSBA seroresponse rates was observed when MenQuadfi was co-administered with Tdap vaccine and HPV vaccine. Antibody responses to HPV vaccine, and to the tetanus and diphtheria antigens in Tdap vaccine, were similar when Tdap and HPV were administered with and without MenQuadfi. Anti-pertussis GMC responses were non-inferior for the pertussis toxoid antigen but did not meet pre-specified non-inferiority criteria for the FHA, PRN, and FIM antigens in Tdap vaccine. Because a serologic correlate of protection for pertussis antigens has not been established, it is unclear if concomitant administration will result in increased susceptibility to pertussis infection. However, an additional analysis demonstrated comparable response rates to each pertussis antigen across study groups, which provides some assurance of adequate pertussis immune responses when MenQuadfi and Tdap vaccines are co-administered.

Clinical Serological Assays

The immune response to the meningococcal A, C, W, and Y components of MenQuadfi was evaluated using a human Serum Bactericidal Assay (hSBA). In addition, the following clinical assays were used in the BLA to measure response the immune response to other vaccines given concomitantly with MenQuadfi: a diphtheria TNA assay, which is a functional assay that measures levels of diphtheria toxin neutralizing antibodies in human sera; ELISA assays that measure anti-tetanus and anti-pertussis antibody responses, and a serology assay that measures immune responses to the HPV quadrivalent vaccine. All the serological assays were deemed to be adequately validated for their purpose.

b). Pediatrics

The Pediatric Study Plan was presented to FDA's Pediatric Review Committee (PeRC) on March 10, 2020. Safety and effectiveness of MenQuadfi have not been established in individuals younger than 2 years of age in the US. A partial waiver from required pediatric assessments of MenQuadfi was granted for infants 0 to <6 weeks of age because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group (vaccinating infants prior to 6 weeks of age would not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age), and MenQuadfi is not likely to be used in this age group. The requirement for assessments in children 6 weeks to 23 months of age (<2 years) was deferred because the candidate vaccine was ready for approval for use in individuals 2 years of age and older before all pediatric studies were complete. The applicant's deferred studies include: Study MET41, to be conducted in infants/toddlers 6 weeks

through 12 months of age evaluating a 4-dose series; Study MET42, to be conducted in infants/toddlers 6 weeks through 18 months of age evaluating a 4-dose series; and Study MET61, to be conducted in infants/toddlers 6 months through 23 months of age evaluating a 2-dose series. The PeRC agreed with the Pediatric Study Plan, including the partial waiver, partial deferral, and the proposed timelines for each study's completion and submission.

Bioresearch Monitoring Review

Bioresearch Monitoring (BIMO) inspections were issued for four US clinical study sites that participated in the conduct of Protocols MET 35, MET 43, and MET 49. The inspections did not reveal any issues that impact the data submitted in the BLA.

c). Pharmacovigilance Review

Since MenQuadfi is a new vaccine and is not licensed in the US or any other country, no epidemiological safety study data were available. The Risk Management Plan for MenQuadfi is version 1, dated December 15, 2018. The applicant notes that there were no unanticipated safety findings or important risks identified during the MenQuadfi clinical trials. Based on the safety profile of similar quadrivalent meningococcal vaccines licensed in the US, the important potential risks are: anaphylaxis, Guillain-Barré syndrome (GBS), and Bell's palsy. There were no cases of any of these three adverse reactions in the completed MenQuadfi clinical trials, except one case of Bell's palsy was reported and classified as unrelated to the vaccine. There have been cases of all three adverse reactions following the other US-licensed meningococcal vaccines. The applicant plans to follow these potential risks with routine pharmacovigilance and review of any related events in the Periodic Benefit-Risk Evaluation Reports (PBRERs). The applicant will also follow-up each report of these three safety concerns with a targeted questionnaire.

The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety Postmarketing Requirement (PMR) study at this time. In addition, pharmacovigilance activities proposed by the applicant in the Risk Management Plan along with adverse event reporting as required under 21CFR600.80 are adequate. The sponsor will also establish a pregnancy registry as a Postmarketing Commitment, along with the following milestone dates: final protocol submission date, the study completion date, and the final report submission date.

7. SAFETY

Safety data were reviewed from 5,118 participants enrolled in six randomized clinical trials (MET43, MET35, MET49, MET56, MET50, and MET44) conducted in the US. These study participants received at least one dose of MenQuadfi and provided post-vaccination safety data. All subjects were observed for 30 minutes after vaccination, with any unsolicited adverse events recorded using an electronic case report form (CRF). Using a diary card, the parent/guardian recorded solicited events through Day 7 postvaccination and all unsolicited adverse events, including medically attended adverse events through Day 30 postvaccination. Using a memory aid, the parent/guardian recorded possible serious adverse events and medically attended adverse events from

Day 30 postvaccination through the end of the study at the Month 6 postvaccination contact. The most frequently reported solicited adverse events following a primary dose of MenQuadfi (occurring in ≥10% of MenQuadfi participants) were as follows by age cohort:

- Children 2 through 9 years of age: injection site pain (38.6%), erythema (22.6%), malaise (21.1%), myalgia (20.1%), swelling (13.8%) and headache (12.5%)
- Adolescents aged 10 through 17 years of age: injection site pain (34.8% & 45.2%), myalgia (27.4% & 35.3%), headache (26.5% & 30.2%), and malaise (19.4% & 26.0%)
- Adults aged 18 through 55 years: injection site pain (41.9%), myalgia (35.6%), headache (29.0%), and malaise (22.9%)
- Adults 56 years of age and older: pain at the injection site (25.5%), myalgia (21.9%), headache (19.0%), and malaise (14.5%)

Comparable rates of solicited adverse reactions were observed in adolescents and adults following a booster dose. The observed proportions of subjects who experienced these solicited adverse reactions were comparable to those observed following Menveo and Menactra in the respective studies. In adults ≥56 years of age, the proportions of subjects who experienced solicited adverse reactions were higher in MenQuadfi (conjugate vaccine) recipients compared to Menomune (polysaccharide vaccine) recipients. Conjugate vaccines are often more reactogenic than polysaccharide vaccines. The rates of unsolicited adverse events in MenQuadfi recipients by age were 28.4% in children 2 through 5 years, 20.2% in children 6 through 9 years, 16.5% in adolescents 10 through 17 years, and 11% in adults 18 through 55 years. The rates of unsolicited AEs were similar to the rates observed in the active comparator group. No deaths were reported in the clinical studies, and no vaccine related SAEs were reported.

Lot Consistency

The applicant satisfactorily demonstrated lot-to-lot consistency based on comparisons of hSBA GMTs elicited by 3 different lots of MenQuadfi. The 3 lots were considered equivalent if for each pairwise comparison of MenQuadfi vaccine lots, the 2-sided 95% CI of the ratio of GMTs was contained within the interval [0.5, 2.0] for each of the 4 serogroups. Lot-to-lot consistency was demonstrated for each serogroup. Safety profiles across lots were consistent.

8. ADVISORY COMMITTEE MEETING

An Advisory Committee Meeting for MenQuadfi vaccine was not held because there were no issues pertaining to this BLA that required input from the Vaccines and Related Biological Products Advisory Committee.

9. OTHER RELEVANT REGULATORY ISSUES

None

10. LABELING

The proposed proprietary name, MenQuadfi, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on June 3, 2019, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on July 16, 2019.

Review team members from APLB reviewed the proposed Prescribing Information (PI), Package label, and Container label on January 13, 2020, and found them acceptable from a promotional and comprehension perspective. Appropriate sections of the revised PI and package/container labels were reviewed for accuracy by clinical, statistical, product, and pharmacovigilance reviewers as well as supervisors and representatives from OVRR management. Recommendations for revisions were collectively provided to the applicant.

The applicant submitted revised versions of all reviewed labeling in agreement with CBER recommendations. During the course of discussions with the applicant regarding the product labeling, the proposed proper name was revised to 'Meningococcal (Serogroups A, C, Y, W) Conjugate Vaccine' in order to minimize the potential for medical errors. We found the carton and container labels submitted in amendment 38 (dated April 14, 2020) and the Package Insert submitted in amendment 39 (dated April 17, 2020) to be acceptable and consider them the Final Draft Labeling. The Applicant will be advised to submit the final content of labeling in Structured Product Labeling (SPL) format after approval.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the BLA, the Review Committee recommends approval of MenQuadfi for the proposed indication and usage.

b) Risk/ Benefit Assessment

Considering the data submitted to support the safety and effectiveness of the MenQuadfi vaccine that have been presented and discussed in this document, the Review Committee agrees that the risk/benefit profile for MenQuadfi is favorable and supports approval in individuals 2 years and older.

c) Recommendation for Post-Marketing Activities

The review committee recommends routine pharmacovigilance with enhanced pharmacovigilance for any newly identified or potential safety issues, as proposed by the sponsor.

PEDIATRIC REQUIREMENT

Sanofi Pasteur is committing to the following clinical studies and milestone dates as planned Postmarketing Requirements to fulfill the Pediatric Research Equity Act (PREA):

1. Deferred pediatric study (MET41) under PREA to evaluate the safety of MenQuadfi in infants and toddlers 6 weeks through 12 months of age.

   Final Protocol Submission: November 9, 2017

   Study Completion Date: August 10, 2022

   Final Report Submission: August 31, 2023

2. Deferred pediatric study (MET42) under PREA to evaluate the immunogenicity and safety of MenQuadfi in infants and toddlers 6 weeks through 18 months of age.

   Final Protocol Submission: November 9, 2017

   Study Completion Date: December 15, 2022

   Final Report Submission: July 13, 2024

3. Deferred pediatric study (MET61) under PREA to evaluate the immunogenicity and safety of MenQuadfi in infants and toddlers 6 through 23 months of age.

   Final Protocol Submission: June 22, 2018

   Study Completion Date: August 5, 2022

   Final Report Submission: February 28, 2023

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

To establish a pregnancy registry (MEQ00070) for MenQuadfi in the United States to collect and analyze the outcome of exposure to MenQuadfi during pregnancy and monitor for any potential safety signals that may arise in this population in routine public health settings.

4. The MenQuadfi® Pregnancy Registry: A Surveillance Registry to assess the safety of MenQuadfi® among Exposed Pregnant Women and their offspring

   Final Protocol Submission: November 30, 2020

   Study Completion Date: June 30, 2028

   Final Report Submission: June 30, 2029