CBER CMC BLA Review Memorandum

BLA STN 125701

MENQUADFI™/ Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

Marcos D. Battistel/Ph.D. /Laboratory of Bacterial Polysaccharides/Division of Bacterial Parasitic and Allergenic Products/Office of Vaccines Research and Review

1. BLA#:STN 125701

2. APPPLICANT NAME AND LICENSE NUMBER

Sanofi Pasteur Inc.

3. PRODUCT NAME/PRODUCT TYPE

MENQUADFI™
Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Vaccine
b. Sterile solution for injection supplied in unit dose vials.
c. The Drug Product active ingredients are the *N. meningitidis* capsular polysaccharides from serogroups A, C, Y, and W135, separately conjugated to tetanus toxoid protein (Drug Substances). The target active ingredients concentrations are 10 mcg of each polysaccharide and approximately 55 mcg of tetanus toxoid protein per 0.5 mL dose.
d. Intramuscular injection.
e. Active primary and booster immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. MENQUADFI is indicated for use in individuals 2 years of age and older.

5. MAJOR MILESTONES

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Marcos D. Battistel OVRR/DBPAP/LBP	Sections 1, 2 and 3 (and subsections within)/CMC
Kathryn Matthias OVRR/DBPAP/LBP Eric Peng OVRR/DBPAP/LRSP	Section 5 Section 5

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
None		

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
04/26/2019	STN125701/0	
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02/10/2020	STN125701/23	
02/14/2020	STN125701/25	
02/28/2020	STN125701/27	
03/13/2020	STN125701/28	
03/19/2020	STN125701/29	
03/27/2020	STN125701/32	
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9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 14171, Amendments 11, 57, 72, 73, 76, 89, 124, 131, 133, 134, and 147	Sanofi Pasteur Inc.			

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

MENQUADFI active ingredients are the capsular polysaccharides (PSs) from *Neisseria meningitidis* serogroups, A, C, Y, and W (MenA, MenC, MenY, and MenW, respectively), separately conjugated to tetanus toxoid (TT), which is used as carrier protein. MENQUADFI is manufactured by combining four monovalent bulk conjugate Drug Substances (DSs), MenA-TT, MenC-TT, MenY-TT, and MenW-TT, respectively. Each of the PSs is purified to yield the PS bulk (b) (4) intermediates, which are subsequently (b) (4) activated. The activated PS intermediates (b) (4) . The manufacturing

process and manufacturing facilities used for the TT carrier protein and for each of the PSs included in MENQUADFI (b) (4) . However, the manufacturing process for the (b) (4) differ from that of the licensed vaccines. MenC, MenY, and MenW are activated and conjugated to TT in (b) (4) using (b) (4) periodate (b) (4) , respectively. MenA conjugation is carried out in (b) (4) . Prior to conjugation, MenA (b) (4) groups are activated with carbonyldiimidazole (b) (4) adipic acid dihydrazide (b) (4). (b) (4) Subsequently, the activated MenA PS is conjugated via (b) (4) to the carrier protein. During the IND phase, Sanofi Pasteur Inc. (Sanofi) communicated to CBER that DS manufacturing would be transferred from Sanofi Building (b) (4) to Building ((b) (4)) in Swiftwater, PA. Therefore, (b) (4), which was used to manufacture DS for MENQUADFI Phase III DP lots, will be discontinued, and (b) (4) will be used to generate the DS to manufacture commercial DP lots. Because of this facility change, CBER requested that Sanofi demonstrate comparability between DS batches and DP batches resulting from (b) (4) DS batches. To support comparability, Sanofi provided manufacturing, release, and stability data for (b) (4) DS batches manufactured in (b) (4) and (b) (4) DS batches manufactured in (b) (4). Additionally, Sanofi provided manufacturing, release, and stability data for (b) (4) DP batches manufactured with (b) (4) DS batches and (b) (4) DP (b) (4), manufactured with (b) (4) DS. Sanofi demonstrated that all the critical process parameters were adequately controlled. All of the batch release data for each DS and each DP batch conformed to the set specifications. The provided data regarding critical process parameters support a controlled manufacturing process with consistent reduction of process-related impurities and process residuals. The data also support comparability between (b) (4) DS batches, as well as for the derived DP lots in terms of the critical quality attributes measured.

However, CBER noted that the stability protocol for the Drug Product was incomplete, and communicated to Sanofi on 26 June 2019, that a (b) (4) test should be included as part of the protocol. CBER explained that as result of the conjugation chemistry used for MenA, MenY, and MenW, the resulting DS is a complex matrix. For example, each PS (b) (4) . Additionally, as a result of formaldehyde detoxification, the TT may be (b) (4) . These confounding factors contribute to (b) (4) and, as a direct consequence, of the DP. As a result of DP (b) (4), the measurement of free PS provides a partial view of potential DP alterations, since it may only be detected after the product underwent other changes such as (b) (4) Thus, measuring free polysaccharide without measuring (b) (4) as part of DP stability monitoring is insufficient. After several rounds of communications, Sanofi agreed to submit a proposal to include (b) (4) test for DP on 17 October 2019.

Sanofi currently uses (b) (4) determination as part of release and stability testing. (b) (4) is also performed as a DP release test. However, among all the parameters that the test provides

(e.g., (b) (4)), Sanofi only reported (b) (4) . As requested by CBER, Sanofi re-evaluated (b) (4) measured parameters to be validated as stability indicating. On 28 February 2020 (STN125701/27), Sanofi provided data demonstrating the (b) (4) is stability indicating and concluded that (b) (4) is not. Sanofi proposed to set the (b) (4) DP release and stability specification for (b) (4) . CBER did not concur with Sanofi's proposal and requested Sanofi to base their specification according to manufacturing capabilities and the available stability data. Sanofi proposed, and CBER concurred, that the (b) (4) DP (b) (4) release specifications would be set to (b) (4) . Whereas the DP stability specification would be set to (b) (4) to ensure (b) (4) will not be below (b) (4) over the DP shelf-life. Additionally, Sanofi committed to introduce an interim control criterion limit of (b) (4) for (b) (4) DP release and stability and to re-evaluate the control limits once more data becomes available.

For DS, Sanofi has requested (b) (4) shelf life under real time storage conditions (b) (4)). To support the proposed shelf life, Sanofi provided (b) (4) stability data under real time conditions for (b) (4) manufactured in (b) (4). However, Sanofi provided only (b) (4) of stability data for commercial (b) (4)-manufactured DS batches. For DP, Sanofi has also requested (b) (4) months shelf-life. To support the request, Sanofi provided (b) (4) months of real time (2-8˚C) stability data, albeit without (b) (4) data, for DP batches manufactured from (b) (4) DS batches, and 18 month of stability data for DP batches manufactured from (b) (4) DS batches. On 28 February 2020 (STN125701/27), Sanofi provided the validation of (b) (4) as stability indicating parameter together with (b) (4) and MenA Free polysaccharide test results for clinical DP batches (b) (4) and for commercial batches (b) (4)). Using all the available MenA Free polysaccharide test result for clinical and commercial DP batches, CBER noticed that the MenA polysaccharide degradation trend together with the current Free polysaccharide release specification (of (b) (4)) would result in batches not meeting stability specification at 24-36 month of storage. Therefore, CBER considers that, at the current Free polysaccharide release specification, and the DP commercial batches being manufactured at (b) (4) of Free polysaccharide content, the appropriate DP shelf life is 36 months at 2-8°C. Moreover, since only (b) (4) of DS stability data are available, CBER also recommends setting DS shelf-life to (b) (4) .

Safety and immunogenicity of MenQuadfi was assessed in five pivotal clinical studies (MET35, MET43, MET49, MET50, and MET56) and three supportive studies (MET28 and MET32) initially developed under IND 14171 (original submission date 02 November 2009). Human complement serum bactericidal assays (hSBAs), considered the "gold standard" for determining protection against invasive meningococcal disease, were used as the primary means of evaluating anti-meningococcal responses in all studies. Additional assays to assess anti-diphtheria, anti-tetanus, and anti-pertussis responses were also utilized in study MET50, in which MenQuadfi

was concomitantly administered with either Tdap (ADACEL) or HPV (GARDASIL) vaccines. Assays included the Diphtheria Toxin Neutralization Assay (TNA), an anti-Tetanus (b) (4) ELISA, and anti-Pertussis (b) (4) ELISAs, including those specific for Pertussis Toxin (PT), Filamentous Haemagglutinin Antigen (FHA), Fimbrial Agglutinogens (FIM), and Pertactin (PRN). All serological assays were validated for use and performance remained consistent throughout the sample testing period. Thus, results obtained from assessing serological responses in clinical studies were considered valid.

We recommend approval of STN 125701 MENQUADFI.

B. RECOMMENDATION

I. APPROVAL

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Marcos D. Battistel, Ph.D./Staff Fellow/DBPAP	Concur	
Kathryn Matthias, Ph.D./ Staff Fellow/DBPAP	Concur	
Eric Peng, Ph.D./ Biologist/DBPAP	Concur	
Willie F. Vann, Ph.D./Supervisory Senior Research/DBPAP	Concur	
Jay E. Slater, M.D./ Supervisory Medical Officer/DBPAP	Concur	

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Module 3

3.2.S DRUG SUBSTANCE
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

(b) (4)

161 pages have been determined to be releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The drug product (DP) vaccine formulation contains each of the four DSs and is prepared as a sterile, aqueous solution containing 30 mM sodium acetate buffer (1.23 mg/dose), (b) (4) and sodium chloride (0.67%, 3.35 mg/dose). Sodium chloride and acetate buffer are excipients used for (b) (4), respectively. Each vaccine dose is of 0.5 mL.

The vaccine is supplied in a 2 mL vial made of Type 1 USP borosilicate glass with a 13 mm opening. The stopper is 13 mm in diameter and made of gray chlorobutyl synthetic polyisoprene blend (latex free), sealed with a 13 mm aluminum seal with plastic flip cap. In order to ensure 0.5 mL/dose, each vial is filled to (b) (4) range. The capsular polysaccharides from each of the four serogroups (A, C, Y, and W135) are the vaccine active ingredients and their target concentration is 10 mcg/dose each. The TT (carrier protein) content is at a ca. 55 mcg per dose and depends on the (b) (4) for the DS used to manufacture the DP.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

DS Physicochemical Properties

The meningococcal polysaccharide components (b) (4)

The DS physicochemical properties are defined by evaluation of the (b) (4) Additionally, as part of physicochemical characterization of DS, PS and (b) (4) are measured and (b) (4) is determined.

The conjugates (manufactured in (b) (4)) also evaluated for clearance of process (b) (4) for MenA (Table 4, page 18, Section 3.2.S.2.5) and (b) (4) for MenC, Y, and W (Table 4, page 18, Section 3.2.S.2.5). The (b) (4) testing are performed as release tests as well.

Table 10: Summary of Drug Product batches manufactured during pharmaceutical development (adapted from Table 2, Section P.2.P.2.3, page 7).

(b) (4)

DS Biological Properties

(b) (4)

3.2.P.2.1.2 Excipients

There are only two excipients used in this vaccine and both are Pharmacopeial grade: Sodium chloride (at 0.67%) and sodium acetate buffer (30 mM, (b) (4)). While sodium chloride is used for vaccine (b) (4), sodium acetate is used for its (b) (4), at which MenA, MenC, MenY, and MenW are more stable.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The DP is formulated as a 0.5 mL unit dose liquid presentation for administration by the intramuscular route. The dosage form of the formulated drug product has not changed throughout development. However, different vaccine formulations were tested in Phase I, II, and III clinical trials. The vaccine was evaluated at different:

a) formulations, to evaluate immunogenicity and
b) dose levels, in order to identify the dosage with optimal results for each serogroup.

From these studies, it was concluded that the vaccine would contain 10 mcg of PS/dose for each serogroup with variable amount of carrier protein dependent on (b) (4).

The following changes were implemented in formulation and dosage of the DP between Phase I and Phase III (see Table 10 for a summary of doses and batches used in each clinical study):

(b) (4)

The excipients (sodium chloride and sodium acetate) in the drug product are added via the sodium chloride and sodium acetate buffer solutions during (b) (4) . Meningococcal polysaccharides are thought to be more stable at a (b) (4) ; therefore, sodium acetate buffer, (b) (4), was used for the drug substances. To ensure that each vaccine vial will contain a 0.5 mL volume, the filled volume is controlled by measuring filled vial (b) (4). The acceptance criterion for fill (b) (4) in each vial is (b) (4) .

3.2.P.2.2.2 Overages

The intended concentration of the final container drug product is (b) (4) batch of Serogroup A, C, Y, and W135. Overages of (b) (4) (MenA) and (b) (4) (MenC, MenY, and MenW) were included to consider any loss during the formulation, filling process, filtration, or due to potential product degradation.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties of the drug product are determined by the release tests on the final container drug product and are described in Section 3.2.P.5.1 Specification(s).

3.2.P.2.3 Manufacturing Process Development

The following Sanofi Pasteur DP manufacturing sites were involved throughout the vaccine development:

- Sanofi (Swiftwater, PA) Building (b) (4) : For Phase I and Phase II DP batches. Formulation was done in (b) (4), except for Formulations I and II that were done in (b) (4). Filling was carried out in Sanofi (b) (4) .
- Sanofi (Swiftwater, PA) Building (b) (4) : For Phase IIb and Phase III DP batches.

The DP batch scale was increased from (b) (4) in Phase I to (b) (4) for Phase II and to (b) (4) for Phase IIb/Phase III DP batches. The batch size was selected to supply vaccine doses for the clinical studies and to support licensure at that process scale. As formulation was moved from process development to manufacturing, the equipment changed from small scale to production scale to accommodate the increase in batch size. For Phases I and II, (b) (4) were used for formulation, the final bulk product was (b) (4) . For Phase IIb and III, a (b) (4) was used for formulation and product was (b) (4) .

Two container closure systems were used throughout development:

a) For Phase I and II, (b) (4) mL USP Type 1 borosilicate glass vials with 13 mm butyl (latex free) stoppers and flip off seals. B
b) For Phase IIb and Phase III, 2 mL vials of the same material were used.

In all the phases of development, albeit with different equipment and bath size, the final bulk vaccine was formulated to final vaccine potency by (b) (4) Formulation and filling were performed under aseptic conditions. After filling, the vials were visually inspected and stored at 2°C to 8°C.

Manufacturing process changes throughout development

The manufacturing process for the Phase III clinical consistency/process validation lots is the same as for the Phase IIb/III GMP lots, except for a change in the (b) (4) .
Sanofi explained that the (b) (4)
Sanofi states the there are no manufacturing process changes between the Phase III clinical consistency/process validation lots and commercial lots.

The following manufacturing steps were investigated during development:

(b) (4)

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

(b) (4)

Filling of the Final Bulk Product

The filling of the final bulk product is performed in aseptic conditions where environmental monitoring and aseptic operating practices are in compliance with the cGMP requirements. The vials are filled to allow a withdrawable dose of NLT 0.5 mL. Studies performed to prove that the filling has no impact on the characteristics of the product include:

- Sterile Filtration ((b) (4)).
  Validation studies were conducted under conditions comprising worst-case conditions for both formulation and filling steps ((b) (4)
  see review for Section 3.2.P.3.5 Process Validation and/or Evaluation).

- Capability of the filling ((b) (4) , see review for Section 3.2.P.3.5 Process Validation and/or Evaluation).

Comparability

A comparability study was performed to ensure that the final container vaccine manufactured using the Phase I through Phase III processes are biocomparable based on the critical quality attributes. However, the specifications changed throughout the development. Free PS changed from (b) (4) in Phase I and Phase II to (b) (4) starting in Phase IIb/Phase III; total protein was not implemented until Phase IIb/Phase III, and the quantitation limit for (b) (4) Free PS varied throughout the development. Moreover, until the vaccine dose was selected in Phase II, the specification for total PS/serogroup also varied between Phase I batches.

Phase I batches: (b) (4)
.

The following release tests were performed for Phase I batches: Sterility ((b) (4) final container), Total PS, Total protein, Free PS, (b) (4), Volume check, Abnormal toxicity, Endotoxin and Physical examination (Table 21, pages 32-33, Section 3.2.P.2.3.

All batches conformed to the specifications set at the time. For (b) (4)
, no (b) (4) Free PS was measured (not implemented) and batches (b) (4)
showed at least one serogroup with (b) (4) Free PS (b) (4) (specification adopted since Phase IIb). However, the (b) (4) Free PS at this initial stage was not greater than (b) (4).

Phase II batch: (b) (4) .
The following release tests were performed for Phase II batches: Total PS, Free PS, (b) (4), Volume check, Abnormal toxicity, Endotoxin, and Physical examination (Table 22, pages 34, Section 3.2.P.2.3. A (b) (4) Free PS specification of (b) (4) was also used for Phase II batches. All batches conformed to their respective release specifications. No deviations were reported.

Phase IIb/III GMP batches (b) (4) **and Phase III batches:** (b) (4) .
The same release tests and specifications were used for Phase IIb and Phase III batches: Total PS, Free PS, (b) (4), Volume check, Abnormal toxicity, Endotoxin, and Physical examination (Table 22, pages 34, Section 3.2.P.2.3). The (b) (4) Free PS specification was tightened to (b) (4) for Phase IIb and Phase III batches. All batches conformed to their respective release specifications. No deviations were reported.

Analytical Process Development

The analytical process for the drug product was developed based on the release tests performed for MENACTRA, as well as (b) (4) guidelines and CBER requests for meningococcal conjugate vaccines. There were no changes made to the sterility, (b) (4), Volume check, Abnormal toxicity, Physical examination (Major A and Major B methods), and specifications throughout analytical development. The Sterility, (b) (4), Volume check, Abnormal toxicity, and Physical examination results for all the DP lots were within established specifications. However, Free and Total PS, Total protein, Endotoxin, (b) (4), and Identity tests were modified throughout the development. The introduced changes are described below.

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

Storage and Transportation

The proposed storage conditions for the bulk and final container DP are (b) (4) at 2°C-8°C, respectively. However, to date there are insufficient data to support (b) (4) shelf-life for the final container DP. There has been no change in storage conditions for the bulk and final container drug product throughout development.

The final container drug product is transferred between manufacturing and storage areas in accordance with the conditions defined in Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls: the DP batches are transported via (b) (4) with a temperature range of 2°C to 8°C equipped with temperature monitoring devices.

3.2.P.2.4 Container Closure System

Sanofi states that the materials of construction of the container closure system were chosen to minimize the likelihood of leaching or absorption from the container closure system.

Type I borosilicate glass vial: this vial has an (b) (4) -treated surface and complies with the (b) (4) USP.

The chlorobutyl synthetic polyisoprene blend (latex free) rubber stopper: the stopper surface is treated with (b) (4) and is compliant with (b) (4) USP.

Compatibility Studies:

Compatibility was evaluated through Extractable/Leachable, Cytotoxicity, and Stability studies. The data provided support compatibility with the container closure system for up to 24 months of storage under normal conditions (2°C-8°C).

Extractable/Leachable Studies

Study 1: The stoppers were subjected to extraction with (b) (4) to potential compounds that could be extracted from the stopper by the DP solution. Samples were analyzed by (b) (4) for detection of extracted (b) (4) from the stopper, respectively.

Study 2: (b) (4) was used to extract compounds from the stopper. Samples were taken and analyzed by (b) (4). Extractable compounds found in the (b) (4) analyses were evaluated and showed no requirement for an additional leachable study.

(b) (4) were detected in the studies from which (b) (4) were found in higher amounts ((b) (4), respectively). (b) (4) was also found at (b) (4). The (b) (4) detected in the extractable study were submitted for toxicology evaluation. (b) (4) was detected below the toxicology threshold of concern of (b) (4) and (b) (4) at (b) (4). Sanofi states that there were no structural alerts, no evidence of genotoxicity concern, and they were below the maximum admissible dose.

Leachables:

The leachables study was performed in two stages. In the first stage, a leachables screening was performed that provided the preliminary leachables data in the product. In the second stage, a long-term leachable study was performed.

The leachables screening study was completed with DP in 2 mL vials. This study evaluated the leachables at the end of 6 months in the normal storage condition (2°C-8°C) and for (b) (4) at an accelerated temperature ((b) (4)). Each sample was analyzed by (b) (4)

The leachables screening study was conducted on (b) (4) tested at time zero and after aging in unit dose vials with products in contact with the latex-free stopper. Vials were stored (b) (4) and control samples pulled from (b) (4). Vials were stored (b) (4) at 2°C-8°C for 24 hours and 6 months, respectively. Controls were stored in (b) (4) vials at 2°C-8°C and vials were stored (b) (4) at (b) (4) for (b) (4); control vials were also stored at (b) (4) for (b) (4).

Overall, no leachable compounds were found to be over the reporting limits for the T0 and 6-month samples. However, Sanofi refers to Table 1, page 6, Section 3.2.P.2.4 for study results, but the referred Table shows the DP batches used for the study and no results are provided. Nonetheless, the more thorough long-term leachables study results were provided (Tables 2-9, pages 7-12, Section 3.2.P.2.4).

Long-term leachables study

The DP was stored in 2 mL serum tubing vials with 13 mm stoppers and flip-off seal under normal conditions (2°C-8°C) for (b) (4) , as well as accelerated conditions (b) (4) as compared to control samples stored in glass vials. The study was performed using three lots of DP (final container lots (b) (4)) and (b) (4) lots of stoppers. Test samples were held (b) (4) in the vials, while control material was stored (b) (4) in (b) (4) vials. The samples were analyzed by (b) (4) was used to quantify (b) (4) , as well as to screen for (b) (4) .
Sanofi provided 24 months of leachables data for DP batches stored at normal conditions (2°C-8°C) and (b) (4) of leachables data for DP batches stored at accelerated conditions ((b) (4)). Samples stored at normal or accelerated temperature conditions showed no leachables levels in excess of safety concern threshold (SCT, (b) (4)). Sanofi reported a maximum of (b) (4) for (b) (4) leachables for DP stored at normal conditions. However, most time points for all the lots yielded results below the reportable level ((b) (4)).
(b) (4) analysis yielded (b) (4) results above the SCT, (b) (4) , but below their respective permitted daily exposure of (b) (4) .

Cytotoxicity Studies

Biological reactivity of (b) (4) with the stopper material were evaluated and Sanofi states that (b) (4) stoppers meet the requirement of the (b) (4) tests.

Development Stability Studies

The stability studies were performed to evaluate DP stability profile and to establish a shelf life. Stability studies were conducted on the current 2 mL and previous (b) (4) mL unit dose vials to test compatibility with the container closure system.

Provided stability data:

1) (b) (4) real time (2°C-8°C) stability data and (b) (4) accelerated stability data (stored at (b) (4)) for DP Phase II batch ((b) (4) , (b) (4) mL glass vial) produced in 2014.

2) The 2 ml vials used during the Phase IIb and Phase III studies are being tested through (b) (4) at 2°C-8°C for the batches produced in 2014 and 2015, respectively. Phase IIb lot (b) (4) was monitored for (b) (4) at 2°C-8°C and for (b) (4) . For

Phase III lot (b) (4) , 36 months of real time stability data and (b) (4) of stability data under accelerated conditions were provided.

For Phase II batch (b) (4) , the following tests and acceptance criteria (in parentheses) were used:

Total PS (between (b) (4) per serogroup)
Free PS (≤(b) (4) per serogroup)
Physical examination (clear, no critical defects)
(b) (4) (report results)
(b) (4)
(b) (4)
Sterility (no growth)
Abnormal toxicity ((b) (4)
Container Closure Integrity (no (b) (4) in test samples)

All results of real time storage conformed to the acceptance criteria and no deviations that would compromise the study were reported. However, it is noted that (b) (4) data is highly variable (Section 3.2.P.2.4, Table 14, page 18). No other trends were observed. However, under accelerated storage, (b) (4) is observed after (b) (4) (Section 3.2.P.2.4, Table 15 page 19).

For Phase IIb and Phase III batches the following tests were performed

Total PS (between (b) (4) per serogroup)
Free PS ((b) (4) per serogroup)
Physical examination (clear, no critical defects)
(b) (4) (report results)
(b) (4)
Sterility (no growth)
(b) (4)
CCIT (integrity maintained)

Phase IIb batch (b) (4) shows ca. (b) (4) increase of Free PS for MenA over a (b) (4) storage at 2°C-8°C. However, all test results for all time points conform to specifications. No other trends were observed for the CQA over the real time stability tested period (Section 3.2.P.2.4, Table 16, page 20). Under accelerated conditions (b) (4) (Section 3.2.P.2.4, Table 17, page 21).
For Phase III batch (b) (4) , all test results for all time points conform to specifications over the 36 months period (Section 3.2.P.2.4, Table 18, page 22). Under accelerated conditions (b) (4) (Section 3.2.P.2.4, Table 19, page 23).
It is noted however, that (b) (4) tests were discontinued for Phase IIb and Phase III batches. On 30 August 2019, CBER requested the re-introduction of (b) (4) test for commercial DP batches on stability.

3.2.P.2.5 Microbiological Attributes

Microbiological control is maintained during the manufacturing process, employing sterile filtration, aseptic filling processes, equipment cleaning and sterilization, clean facility design, and environmental monitoring. During manufacturing, controls are in place to ensure sterility of the (b) (4) filled Drug Product. All equipment used in the manufacturing process is sterilized prior to use and the product flow path disposables provide a closed system for product movement from the bulk (b) (4) to the filling line. The final bulk is stored at (b) (4) is intended to prevent environmental ingress into the storage vessel. Stability studies performed at actual storage conditions ((b) (4)), demonstrate that the container closure system maintains product sterility over the (b) (4) (Section 3.2.P.8.3).

Media Hold Study for the (b) (4) Drug Product

The media hold study completed in the (b) (4) demonstrated the sterility of material stored in (b) (4) All results conformed to specifications (Table 2, Section 3.2.P.2.5, page 5).

Container Closure and Package Integrity Unit Dose Vials

The validation consisted on manufacturing filling ca. (b) (4) vials filled with (b) (4) on Line (b) (4), Building (b) (4), and a total of (b) (4) collected from the (b) (4) of each supplier run were visually inspected. Out of the (b) (4) vials, a total (b) (4) vials were randomly selected and used as test samples, with (b) (4) samples as controls in the (b) (4) test.

Table 2, Section 3.2.P.2.5 shows that all vials pass the CCIT, supporting the use of the 2 mL borosilicate Type I borosilicate glass vial, 13 mm stopper, 13 mm flip cap combination on the Line (b) (4) filler and capper.

3.2.P.2.6 Compatibility

The vaccine is a ready-to use formulation. There is no reconstitution, dilution, or administration with other dosage devices. Therefore, no compatibility study other than that with the container closure system is required.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Manufacture and Testing: Sanofi Pasteur Inc (registration # 1725), Discovery Drive Swiftwater, PA 18370, USA.

DP formulation: (b) (4).
Filling of unit dose vials: (b) (4), line (b) (4).
Packaging of unit dose vials: (b) (4).
Release and Stability testing: (b) (4).

Testing: Sanofi Pasteur Inc (b) (4) (*in vivo* stability testing).

3.2.P.3.2 Batch Formula

(b) (4), (b) (4), to produce bulk vaccine. Although the intended concentration of the final container DP is (b) (4), the DP is formulated to contain (b) (4) batch of MenA ((b) (4) overage) and (b) (4) batch of MenC, MenY, and MenW ((b) (4) overage), respectively. The approximate concentration of carrier protein is (b) (4), which depends on the (b) (4) for each DS. To obtain target concentrations, the DSs are (b) (4). The (b) (4) yields ca. (b) (4) unit-dose vials (ca. (b) (4) mL per vial to ensure 0.5 mL per dose).

3.2.P.3.3 Description of Manufacturing Process

Final Bulk Manufacturing Process:

The manufacturing process (Section 3.2.P.3.3) is divided in (b) (4) steps:

(b) (4)

(b) (4)

Unit Dose Vial Manufacturing Process:

The manufacturing process is divided in five steps summarized below:

Step 1: (b) (4)

Step 2: The 2 mL type 1 borosilicate tubing vials are (b) (4) rinsed and depyrogenated and processed through a conveyor for use in filling.

Step 3-Filling: The 2 mL vials are filled to a final (b) (4) between (b) (4) (CPP, to ensure a 0.5 mL extractable dose) and stoppered with 13 mm latex free, chlorobutyl sterile stoppers. Vials are (b) (4) by an In-Process Check (IPC) system. A sample is taken to measure (b) (4) (IPC, (b) (4) acceptance criterion).

Step 4-Sampling: All vials are inspected. Samples of unlabeled vials are taken for release testing.

Step 5-Inspection and Storage. Inspected vials are placed in cold storage at 2ºC to 8ºC.

Inspection, Labeling and Packaging

All vials are inspected (manually or automatically). Vial defects are classified as Critical, Major, and Minor. The inspection acceptance criteria are:

Critical Defects: (b) (4)

Major Defects acceptance quality level (AQL)= (b) (4)
Minor Defects AQL= (b) (4)

Unit dose vials are removed from storage, transported to the packaging area, labeled, and packaged in Building (b) (4). The labels and packaging components are released by Sanofi's Quality Department prior to use. The packaged Drug Product is placed in cold storage at 2ºC to 8ºC.

Transport and storage
The filled Drug Product is transferred between manufacturing, storage areas, or distribution centers via a (b) (4) with a temperature range of 2°C to 8°C equipped with temperature monitoring devices. Time-out-of-Refrigeration (TOR) is documented in the batch record for each step of the inspection and packaging process to ensure that product does not exceed the TOR limit. The final labeled and packaged product is stored at 2°C-8 ºC under restricted card access.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The CPP and controls are described and reviewed in Section 3.2.P.3.3

There are no intermediates in the production of the Drug Product.

3.2.P.3.5 Process Validation and/or Evaluation

The validation studies aimed to demonstrate that the formulation and filling processes consistently produced a product that met the pre-determined criteria for safety, potency, purity, and quality. The clinical consistency/process validation lots were manufactured with DS material manufactured in Building (b) (4). However, the DS manufacturing process has been transferred from (b) (4). Thus, Sanofi provided a supplemental lot manufactured from DS from (b) (4) to demonstrate comparability. Additionally, Sanofi introduced a DP manufacturing change for the supplemental DP lot: the (b) (4)

Process Validation for the Drug Product Bulk Formulation Process

(b) (4)

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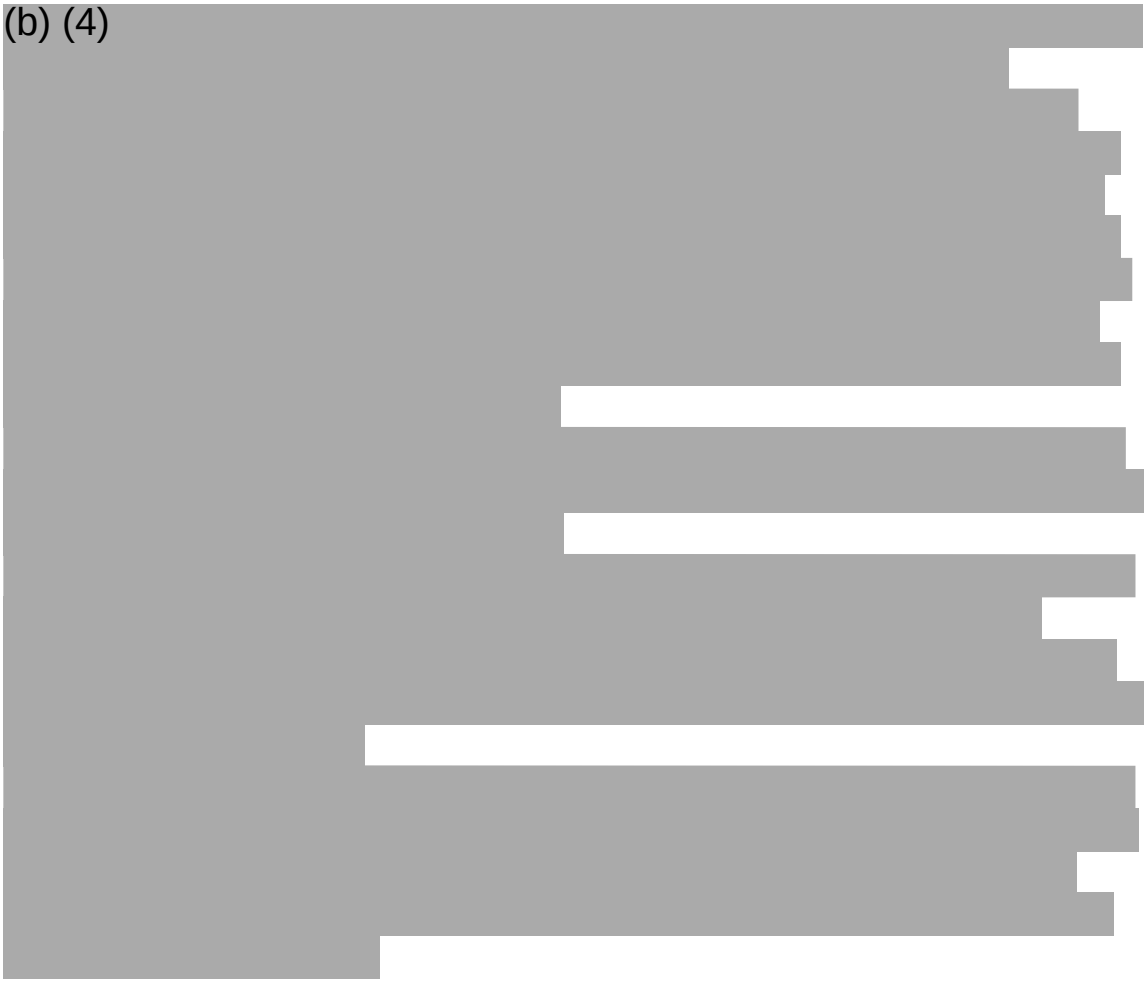
(b) (4)

Process Validation for Drug Product Unit Dose Vials
For the (b) (4) DP, the following stages were evaluated:

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



3.2.P.4 Control of Excipients

The excipients used for the drug product are:

Sodium Chloride, (b) (4)
Sodium Acetate (b) (4)
(b) (4)

3.2.P.4.1 Specifications

Sodium Acetate, (b) (4): prepared with sodium acetate (b) (4)
Sodium chloride (b) (4). The excipients tested according to a pharmacopoeia monograph.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

The analytical procedures used for excipients are those described in the pharmacopoeial monographs. Compendial methods provided within pharmacopoeia do not require validation.

In addition to supplier testing, Sanofi performs the following tests on the excipients:

Sodium Chloride, (b) (4)
(b) (4)

Sodium Acetate (b) (4)
(b) (4)

(b) (4)

3.2.P.4.4 Justification of Specifications

Justification of specification was not provided since it is not required; excipients used comply with a pharmacopoeia.

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal origin are used during the manufacture of the drug product.

3.2.P.4.6 Novel Excipient

No novel excipients are used during DP manufacturing.

3.2.P.5 Control of Drug Product
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Formulated Drug Product (Bulk)

- (b) (4): is a compendial test ((b) (4)) and the acceptance criterion is (b) (4) .

Unlabeled Final Container Drug Product

Non Compendial Release Tests

Total PS: (b) (4) 10 mcg/mL (b) (4) for each serogroup. Total PS is tested for release and as part of the stability program. Total PS content is determined to ensure that the material has been formulated correctly. The test method and acceptance criteria for stability are identical to those applied at release. The specification range is based on the (b) (4) target PS concentration and is consistent with process and method variability for this product.

- Free PS: (b) (4) product is tested for Free Polysaccharide at release, and as part of the stability program. The test method for stability is identical to the release test. The release specification of (b) (4) ensures that the drug product will remain within the stability specification of (b) (4) throughout the shelf-life while in the final container. The difference in release and stability specifications is consistent with other vaccines, such as MENACTRA.

- Total protein: between (b) (4) . The upper and lower limits of this specification are defined based on expected protein limits necessary for acceptable (b) (4)).

- Physical appearance:
  Major A (major defects: (b) (4) ; minor defects: (b) (4))
  The AQL inspection is the visual examination of the container, closure, and product for defects. A major defect is not critical (may affect the product itself), but decreases the usability of the product or deemed unacceptable by the user. A minor defect affects the appearance, but not the form, fit, or function. All vials are inspected, and the percentage determined.
  Major B (rejects-(b) (4)).
  The test evaluates (b) (4)

- (b) (4)

Compendial Release Tests

- (b) (4)
- Endotoxin: (b) (4). The endotoxin limit specification is based on the threshold pyrogenic dose for a 2-year-old child, consistent with (b) (4).
- Sterility: No growth. The specification conforms to (b) (4).
- Volume Check: NLT 0.5 mL/vial. The specification was set to ensure that the extractable volume is 0.5 mL (dose volume).

Labeled Final Container Drug Product

- Identity (non-compendial): Identifies positive for each of the four serogroups (A, C, Y, and W), positive for TT, and negative for (b) (4).
  Every lot of final container drug product unit dose vial is tested for identity after all labeling and packaging operations have been completed. The test ensures the identification of the product in a multi-product facility.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

- **Bulk Drug Product**

(b) (4)

(b) (4)

- **Unlabeled Final Container Drug Product**

Total Polysaccharide, by serogroup (Q_0578298)
Total polysaccharide content analysis involves (b) (4)

Validation (Q_0635191 for MenA, Y and W and Q_0515377 for MenC): Total PS test was evaluated for Accuracy, Precision (repeatability and intermediate), Specificity, Linearity, Range, and Robustness for the unlabeled final container DP. During development, the method was validated for all four serogroups. However, method changes were implemented that required re-validation:

(b) (4)

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(b) (4)

(b) (4) **Free Polysaccharide, by serogroup (Q 0578298)**

The protein-PS conjugate is (b) (4)

Total PS for each of the four serogroups is calculated as the (b) (4) in mcg/mL. Free PS for each serogroup is calculated as the (b) (4) in mcg/mL and is compared against the total PS concentration (mcg/mL) result to yield a (b) (4) of free PS.

For the (b) (4) suitability test, a (b) (4) . A positive control is also tested with the samples to monitor sample performance during the run.

These criteria also apply for total PS determination:

(b) (4)

(b) (4) The (b) (4) should remain constant unless there is (b) (4).

Validation (Q_0635191 for MenA, Y and W and Q_0520205 for MenC): As for the Total PS test, the Free PS test was evaluated for Accuracy, Precision (repeatability and intermediate), Specificity, Linearity, Range, and Robustness for the unlabeled final container DP. The Free PS test was evaluated in the range (b) (4)

In addition to the standards used for Total PS validation, (b) (4) PS standards were used to represent Free PS in this validation and is representative of the type of Free PS that is generated as the conjugates (b) (4) (Table 5, page 14, Q_0635191 and Table 11, page 20, Q_0520205).

(b) (4)

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

(b) (4)

The method is considered validated. However, Sanofi provided summary results for MenC total and Free PS tests determination (Section 3.2.P.5.3), but did not provide the validation data, arguing that the tests for MenC were already validated during a previous validation campaign. For completeness, the validation data has to be submitted to be evaluated by CBER.

Total Protein (Q_0578617, (b) (4))

The (b) (4) measures the total protein content utilizing (b) (4)

The test is valid if: (b) (4)

Validation (Q_0604074): The method was evaluated for Precision (repeatability and intermediate), Accuracy (inferred by recovery of expected protein concentration), Linearity, Specificity, QL, and Range.

(b) (4)

(b) (4)

Bacterial Endotoxin (by (b) (4), Q_0233845, (b) (4))
This test is performed in compliance with the (b) (4) . The (b) (4) assay employs an (b) (4)

(b) (4)

Validity criteria: (b) (4) criteria: (b) (4)

Volume Check

Volume check is performed in compliance with (b) (4) unit-dose vials are (b) (4) selected. Its contents are drawn from syringes (b) (4). The volume is calculated knowing solution (b) (4).

Physical Appearance:

- **Major A (Q_0281004):** The sample is visually examined to detect the presence of particulate or foreign matter or unusual product appearance, defined as different from the description of product. The sample is also examined for cosmetic-type defects, such as (b) (4) the whole batch is rejected.

- **Major B (Q_0277655) :** the product is examined against a (b) (4) to confirm that the solution remains (b) (4), exhibiting no non-characteristic (b) (4). In addition, the product is tested for (b) (4) to assess (b) (4) of the Major B defects (rejects) is compared to the product specification value. (b) (4) the whole batch is rejected.

(b) (4)

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- **Labeled Final Container Drug Product**

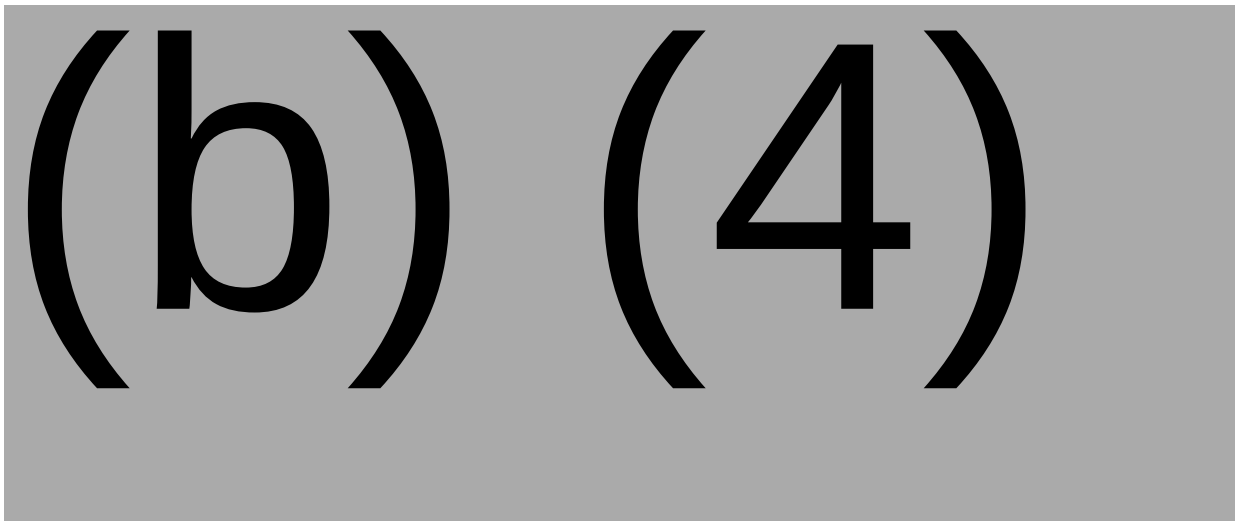
  Identity (Q_0578457, (b) (4))
  (b) (4) to each meningococcal polysaccharide serogroup and the TT carrier protein are used to determine the presence or absence of (b) (4) PS and carrier proteins in the test sample. Appropriate controls are included to validate the specificity of each test run. The following controls are used: (b) (4)

3.2.P.5.4 Batch Analyses

Sanofi provided batch analysis data for (b) (4) DP batches manufactured from DS from (b) (4) (Phase III clinical consistency/process validation Bulk batches (b) (4)) and (b) (4) DP batch from DS from (b) (4) (Bulk DP batch (b) (4)). All DP batches were formulated in (b) (4) using Formulation Skid (b) (4) at (b) (4), using the same manufacturing process. Phase III DP batches were manufactured in March 2016 while the supplemental batch was manufactured in June 2018. These bulk DP batches were used to manufacture final container unit dose vial batches in (b) (4) line (b) (4). Phase III unit dose vials ((b) (4)) were manufactured in April 2016, whereas the supplemental batch unit dose vial was manufactured in July 2018 ((b) (4)). The batch information is provided in Table 1, page 4, Section 3.2.P.5.4 Batch Analysis. The batch genealogy from DS batches to each final container DP batch is summarized in Table 11 below.

Release Tests Results:

Bulk Drug Product
(b) (4)



Final Container Drug Product (Unlabeled Unit Dose Vial)

The following release tests were performed on the Final Container Drug Product batches ((b) (4)): Abnormal Toxicity, Volume Check, (b) (4), Sterility, Bacterial Endotoxin, Total Protein, Total Polysaccharide, (b) (4) Free Polysaccharide, Physical Examination (Major A and Major B), (b) (4) , CCIT. All test results conformed to their respective specifications and no deviations were reported. Moreover, the release tests results for DP batch (b) (4) are comparable with those obtained for (b) (4) . Therefore, the data supports equivalency between DP batches manufactured with (b) (4) DS batches (Phase III batches) and the DP batch manufactured with (b) (4)-manufactured DS batches (Commercial batch). However, there were specification changes between Phase III and Commercial DP batches:

a) The specification for Total protein was changed from (b) (4) for licensure. CBER concurred with the proposal to a change in the total protein specification in a response to Amendment 82 (IND 14171) dated 6 December 2016. Regardless of the specification used, the produced batches yielded a (b) (4) total protein concentration.
b) (b) (4) test was introduced for Commercial DP batches, starting from batch (b) (4). Therefore, the specification of (b) (4) was set only for Commercial DP batches. The addition of (b) (4) adds an additional level of control of the DP manufacturing process and DP quality.
c) The quantitation limit ((b) (4) Free polysaccharide) was re-assessed and now is expressed in (b) (4) instead of (b) (4) . As a result, values below (b) (4) were reported as (b) (4) for Phase III DP batches. For the Commercial batch, the reported values adopted the new quantitation limit expressed in mcg/mL. Therefore, values below (b) (4) Free polysaccharide can be reported according to the quantitation limit for each serogroup. This re-expression of (b) (4) Free polysaccharide does not impact the set specification.

Sanofi summarized batch analysis data for Final Container DP in Section 3.2.P.5.4, page 9-10.

Final Container Drug Product (Labeled Unit Dose Vial)

Sanofi performs Identity tests in the labeled unit dose vials to ensure product identity. Sanofi provided the certificate of analysis for batches (b) (4) . All batches were identified positive to TT, MenA, MenC, MenY, and MenW polysaccharides and negative for (b) (4) (the release data are summarized in Table 4 page 11, Section 3.2.P.5.4). All the certificate of analysis for the MET43 batches were provided and can be found in Section 3.2.P.5.4. However, since labeling of the unit dose vial was not performed for the commercial batch, no information was provided. Sanofi has to provide the release data and batch number for the commercial batch.

3.2.P.5.5 Characterization of Impurities

Most impurities that can be found on the product result from impurities present in the (b) (4). Impurities characterization was performed on the (b) (4) and was reviewed in Section 3.2.S.3.2 of this memo.
However, the presence of impurities was also tested on the DP. Endotoxin testing is performed on the final container DP to demonstrate absence of the potential impurity. Moreover, Section 3.2.P.2.4 describes Extractable/leachable studies (potential impurities from and compatibility with the container closure system), cytotoxicity studies, and stability studies (reviewed in Section 3.2.P.2.4 of this memo).

3.2.P.6 Reference Standards or Materials

Sanofi states there is no drug product reference standard used for the DP.

3.2.P.7 Container Closure System

I defer to the DMPQ reviewer for evaluation of this section.

3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Drug Product Bulk

(b) (4)

(b) (4)

Final Container Drug Product (Unlabeled Unit Dose Vial)

The Bulk DP for Phase III clinical consistency/process validation lots (b) (4) were dispensed from (b) (4), while the supplemental GMP lot (b) (4) was dispensed from a (b) (4). The Drug Product unit dose is filled into a 2 mL USP Type I borosilicate clear glass vial with 13 mm butyl (latex free) stopper and a 13 mm flip-off seal.
Sanofi provided stability data for the DP stored under real time (5°C ± 3°C) and accelerated storage conditions ((b) (4)) for batches (b) (4) (used in Phase III) and batch (b) (4) (Supplemental).
The following tests performed for stability monitoring of DP stored at 5°C ± 3°C: Total and Free PS, Physical examination, (b) (4), Sterility, Specific Toxicity and CCIT.
The stability protocol includes batch testing at release, and at 1, 3, 6, 9, 12, 18, 24, 30, 36, (b) (4) of storage, except for Sterility (performed at 0, 36, (b) (4)), and Specific Toxicity and CCIT (performed at 0, 12, 24, 36, (b) (4)). It is noted that the stability specification is (b) (4) Free PS, whereas the specifications for all other tests remain the same as for the release tests. The Free PS specification (b) (4) is unacceptable since the shelf-life of the product has to ensure the (b) (4) Free PS content remains (b) (4) throughout the DP shelf-life. Further, (b) (4) Free PS has remained (b) (4) for the manufactured batches to date. Therefore, there is no justification for the proposed specification for stability monitoring. Sanofi should also consider tightening the specification for release testing, as well. An IR was sent to the company and is described below.

For DP stability monitoring, when stored under stressed conditions ((b) (4)), the same set of tests as for DP stored at (5°C ± 3°C) are performed, except for Specific Toxicity, which is not performed.
The stability protocol includes batch testing at release, and at (b) (4) of storage, except for Sterility and CCIT Sterility (performed at (b) (4)).

Sanofi provided 36 months (out of (b) (4) planned) of real time stability for Phase III batches (b) (4) stability data when DP is stored at (b) (4) planned, completed). Out of the QA measured for stability, an increase

of (b) (4) Free PS is observed. For all Phase III batches, (b) (4) Free PS ranges between 1(b) (4) at the 36 months time point, while at release the (b) (4) Free PS values were (b) (4) (Tables 11-13, page 13-16, Section 3.2.P.8.3). Thus, results obtained beyond 36 months of storage may not yield (b) (4) Free PS values that conform to batch release specifications. Moreover, under stressed conditions, (b) (4) , compared to their respective release values (Tables 15-17, page 17-19, Section 3.2.P.8.3). The remaining stability indicating tests remained invariant during the tested period. No deviations were reported.

For supplemental lot (b) (4), Sanofi provided 9 months (out of (b) (4) planned) of real time stability and (b) (4) stability data when DP is stored at (b) (4) (out of (b) (4) planned, completed). At 3 months of storage at 5°C ± 3°C, an increase, although within specification, of Total PS for MenY and MenW was observed. The increase on Total PS was attributed to the robustness of the method. Previous and subsequent time points do not show same high Total PS values, so the results are consistent with method variability or experimental mistake. All other QA measured remained invariant for 9 months of storage at 5°C ± 3°C. As observed for Phase III DP batches, a significant (b) (4) is observed for (b) (4) PS under stressed conditions (Table 18, page 20, Section 3.2.P.8.3).

The release tests performed on MENQUADFI were compared to other similar vaccines (see Table 12, next page). It can be noted that Sanofi does not monitor either (b) (4) during stability while these tests are currently performed for MENACTRA (measures (b) (4)) and MENVEO (measures (b) (4)) and provide additional assurance that the conjugate is not negatively impacted during storage.

On 26 June 2019, CBER issued an information request, to which Sanofi responded on 19 July 2019 (IND 125701/4). CBER questions and Sanofi's answers are summarized below:

Question 1:
In Section 3.2.P.8 Drug Product Stability protocol, you include Total Polysaccharide, Free Polysaccharide, (b) (4), Physical Examination, Sterility and CCIT tests (with respective acceptance criteria). We note that (b) (4) is used to measure (b) (4) in the post approval stability protocol for the MenA, C, Y and W135 (b) (4), but not for Drug Product.
a. Please include a test for (b) (4) in the stability protocol of your Drug Product (b) (4) Unit Dose Vial.
b. Please provide all available (b) (4) stability data for batches (b) (4) .

Answer to Question 1:
Sanofi stated that CBER agreed on 14 March 2016 (IND 14171/89) for Sanofi to remove the (b) (4) test from the stability protocol. Therefore, Sanofi did not collect (b) (4) for Phase III DP batches, nor for the commercial DP batch.

Table 12. (b) (4) DP stability tests performed on meningococcal licensed conjugate vaccines. The license number and the company that developed the vaccine are shown in the table.

DP Stability Tests	**MENVEO (125300, GSK)**	Appearance	(b) (4)	Total PS	Free PS		(b) (4)	Sterility							
	MENACTRA (125089, Sanofi)	Physical app.		Total PS	Free PS	(b) (4)		Sterility	Specific Toxicity						
	Menhibrix (MenCY and Hib TT conjugate: 125363, GSK)	Description		Total PS		(b) (4) distribution (b) (4)		Sterility	GST	Endotoxin	Water content				
	ActHIB (Hib TT, 103935, Sanofi)	Appearance		Total PS	Free PS	(b) (4)		Sterility	Abnormal toxicity	Endotocin	Residual moisture	CCIT	Pyrogens		
	MenQuadfi (125701, Sanofi MenACYW-TT)	Physical exam.		Total PS	Free PS			Sterility	Specific Toxicity			CCIT			

Question 2:
Please provide the most up-to-date stability data for the process validation and commercial Drug Substance and Drug Product batches as they become available. Per question 1 above, please include a measurement of (b) (4) *in the stability data for Drug Product and Drug Substance.*

Answer to Question 2:
Sanofi provided the 36-month stability data for the Phase III DP batches and 9 month stability data for the commercial DP batch. These data are reviewed in Section 3.2.P.8.3.

Question 3
Please submit batch records for the (b) (4) *Drug Product batches included in this submission:* (b) (4) *(Phase III Consistency/Process Validation) and* (b) (4) *(Commercial).*

Answer to Question 3:
Sanofi provided batch records for the (b) (4) bulk DP batches and batch filling records for the (b) (4) final container batches, as requested. The batch production and batch filling records are reviewed in Section 3.2.R.

Question 4
Please submit batch records for the Drug Substance batches (b) (4) *(serogroup A),* (b) (4) *(serogroup C),* (b) (4) *(serogroup Y) and* (b) (4) *(serogroup W135) that were used to produce the Commercial Drug Product batch* (b) (4).

Answer to Question 4:
Sanofi provided batch records for the (b) (4) DS batches that were used to produce Drug Product batch (b) (4). The batch production records are reviewed in Section 3.2.R.

As a result of Sanofi's answer to Question 1, CBER issued its response to Sanofi on 30 August 2019. CBER questions and Sanofi's answers are summarized below:

On June 26, 2019, we issued an Information Request letter (IR) requesting the following: a) Please include a test for (b) (4) *in the stability protocol of your* (b) (4) *Drug Product Unit Dose Vial, and b) Please provide available* (b) (4) *stability data for batches* (b) (4) .
In your response to these questions in amendment 4 (sequence 0005) dated July 19, 2019, you state that per CBER advice/memo dated December 6, 2016, you implemented (b) (4) *for final container Drug Product release testing only, and not for stability. However, we have determined that our answer in the December 6, 2016 communication (Response 4) was in error. Considering that a* (b) (4) *test is already implemented for* (b) (4) *Drug Product Unit Dose Vial release:*

a. Please include a test for (b) (4) *in the stability protocol of your* (b) (4) *your Drug Product Unit Dose Vial.*

b. In addition to the tests in your stability protocol, please begin monitoring (b) (4) *in the stability protocol for Drug Product batches* (b) (4) .

c. Since (b) (4) *was not measured for Drug Product batches* (b) (4) *, except at release, please place* (b) (4) *new Drug Product batches on stability following the stability protocol that includes* (b) (4) *testing.*

Answer to Questions a, b, and c:
Sanofi responded informally via email on 20 September 2019 and provided the technical report Q_0545841. The developmental stability study in the report tracked (b) (4) and free polysaccharide of Drug Product over time, and while free polysaccharide was observed to (b) (4) for all serogroups, the (b) (4) did not change in a quantitatively significant way. However, in the report a significant change on the (b) (4) was observed for batches stored under (b) (4) conditions compared to the DP stored at the recommended storage temperature (Figure 3 and Figure 4, page 14, Q_0545841). In contrast, the reported (b) (4) obtained from these significantly different (b) (4) yielded similar values. Therefore, Sanofi concluded that (b) (4) is not suitable for DP stability monitoring.
The reviewer does not concur with Sanofi's rationale since the pronounced (b) (4) changes should be reflected in the obtained (b) (4) values. Therefore, CBER issued an IR letter dated 15 October 2019 and scheduled a teleconference for 17 October 2019. CBER questions are presented below:

Question 1:
We do not concur with your plan to not include a test for (b) (4) *as part of your DP stability protocol. The test allows for additional physicochemical characterization that is not provided by any other stability test currently in your DP stability protocol, including free polysaccharide. Free polysaccharide determination is blind to* (b) (4) *alterations and as a result, it does not necessarily reflect all the changes that the DP can*

undergo during storage. For example, (b) (4) *A proper* (b) (4) *data analysis should reflect the radical changes observed in the* (b) (4) *presented in document Q_0545841, Figures 1, 3 and 4, pages 9 and 14, respectively.*

Upon discussion during the 17 October 2019 teleconference, Sanofi agreed to add (b) (4) as part of DP stability protocol, as well as to provide a plan for implementing (b) (4) as a stability indicating parameter. Sanofi committed to submit the plan 15 November 2019. CBER concurred.

Question 2:

(b) (4)

Question 3:

(b) (4)

(b) (4)

Question 1: *In Section 1.11.1 Table 1, page 5, in addition to the Process Validation/Phase III and Commercial batches (*(b) (4) *) you propose to provide stability data for DP batches* (b) (4) *. However, we do not have batch genealogy, release or stability information for DP batches* (b) (4) *to assess the relevance of the data collected from these proposed batches.*
Please provide for each of the following DP batches: (b) (4) *:*

a) Batch genealogy, including DS and DS intermediate batches used to manufacture each DP batch, batch scale, site of manufacturing and their corresponding manufacturing dates.
b) Batch release data for each of the DS batches used to manufacture each of the DP batches.
c) All the stability data collected on these DP batches.

Sanofi provided the requested data. However, it was noted (STN 125701/22, Section 1.11.1, Table 1, page 7) that DP batches (b) (4) were manufactured at a larger scale ((b) (4)) than the Commercial DP batch (b) (4) and the clinical batches (b) (4) . Therefore, data from batches manufactured at a different scale cannot be considered in support of DP expiry. The stability data provided conform to the set specifications. Expectedly, MenA free polysaccharide tend to increase during storage at 2°C-8°C. However, the values remain within the not more than (b) (4) free PS specification for the tested period ((b) (4) for clinical DP batches (b) (4) and for up to 12 months for DP batches (b) (4)). No other significant trends were observed for the monitored stability indicating parameters.

In response to CBER IR dated 30 August 2019 (STN 125701/22), Sanofi committed to provide (b) (4) data for DP lots by 31 January 2020 for the stability samples pulled on November 2019 and by 15 March 2020 for the samples pulled in January 2020. However, Sanofi provided the DP stability data for both samples, those pulled in November and those pulled in January in STN 125701/22 (31 January 2020).
Sanofi provided (b) (4) stability data for DP batches (b) (4) (0, (b) (4) months), (b) (4) (0 and 18 months), and (b) (4) (0 and 12 months) stored at 2°C-8°C. Sanofi also provided stability data for other DP batches. However, these additional batches were manufactured at a larger scale and are not considered supportive of DP stability. The provided data included (b) (4) As scheduled according to the stability protocol, Sanofi also provided (b) (4) Free PS content at the mentioned time points. The (b) (4) for batches (b) (4) show (b) (4) at time zero (Figures 10, page 13; Figure 12, page 15; Figure 14, page 17; Figure 16, page 19; Figure 18, page 2). The (b) (4) was only present at time zero. Sanofi explained that the (b) (4) Sanofi stated that moving forward, the column will be dedicated for the assay and that the correct (b) (4) appearance will be confirmed before implementation of the (b) (4) . The described issue does not appear to impact the measured (b) (4) parameters and, more importantly, the (b) (4) collected on samples at later storage time points yielded adequate (b) (4) . Therefore, the reviewer considers that the described issue does not impact the validity of the data for their consideration to support DP expiry dating.

Question 2: *Considering that you will be providing validation of your* (b) (4) *assay in February 2020;* (b) (4) *data for process validation and commercial DP batches cannot be considered in support of product expiry until the assay has been adequately validated. Please acknowledge.*

Sanofi acknowledged.

Due to deficiencies identified in STN 125701/22 CBER issue an IR on 7 February 2020. Sanofi answered on 14 February 2020 (STN 125701/25). CBER questions and Sanofi's answers are summarized below:

Question 5: *In Section 1.11.1, Response to IR dated December 9, 2019, Table 1, page 7 we note that Bulk DP batches* (b) (4) *were manufactured at* (b) (4) *rather than the* (b) (4) *scale for the clinical and comparability batches (*(b) (4) *) that were presented in the original BLA submission. Therefore, these larger scale batches cannot be used to support DP expiry dating because comparability between DP batches manufactured at* (b) (4) *production scales has not been demonstrated. Please acknowledge.*

Sanofi acknowledged that data from DP batches manufactured at (b) (4) scale cannot be used in support of DP expiry.

Question 6: *In the current submission, you did not provide release data for the final container DP batches* (b) (4) *. To evaluate the suitability of the data provided to support final container DP expiry dating, we need final container DP batches release data.*
a. Please confirm that you will be providing all release test results for final container DP batches (b) (4) *, in addition to the agreed upon stability data in you upcoming February submission.*

Sanofi provided the release data for batches (b) (4) in the STN 125701/25 submission (Section 1.11.1 Table 1, pages 6 and 7). All data conform to specifications.

Question 7: *In the provided* (b) (4) *validation data (document SWT-REP-021709) you did not include data regarding the use of* (b) (4) *as a stability indicating parameter. On November 15, 2019, you submitted a plan) to validate* (b) (4) *as stability-indicating parameter and to perform an analysis for determining release and stability acceptance criteria.*
a. Please confirm that the target submission date for these data is February 28, 2020.
b. Please confirm that the validation of (b) (4) *as a stability indicating parameter will be included in the upcoming amendment scheduled for February 2020. These data should include samples that have been* (b) (4) .

Sanofi confirmed that the report containing data in support of using (b) (4) for release and stability is still planned for 28 February 2020. Moreover, Sanofi stated that the report will include current assessment of the stability-indication of the (b) (4) result. Based on the results, the study will also provide information to derive a relevant specification for (b) (4) at release and for stability.

Question 8: *As a reminder, in all future amendments relating to DP stability assay validation, please include the* (b) (4) *in addition to all other stability test results for all DP batches that you will use to support expiry dating.*

Sanofi agrees to provide (b) (4) in all future amendments

regarding drug product stability test results that will be used to support expiry dating.

We have the following question regarding your responses to our information request dated August 30, 2019:

Question 9: *You present* (b) (4) *for* (b) (4) *final container DP lots* (b) (4) *(pages 7-20). None of these* (b) (4) *show a change in* (b) (4) *response during DP* (b) (4) *as was observed for* (b) (4) *batches (amendment 12 Section 1.11.1 document* (b) (4) *Data). Please clarify why there is no significant change in* (b) (4) *response in the provided* (b) (4).

Sanofi explained that the (b) (4) software scales (b) (4) responses relative to the (b) (4). Since (b) (4) for DP is more (b) (4). Sanofi provided rescaled representative (b) (4), showing a zoomed view of the (b) (4).

Sanofi satisfactorily responded to CBER questions and complied to CBER requests.

Drug Product shelf-life determination:

To decide an appropriate shelf-life for DP batches stored under real time conditions (2°C-8°C), we evaluated the trend observed for the available stability indicating parameter (b) (4) Free PS as a function of storage time. Since MenA is the most labile PS out of the four serogroups, MenA was used as the worst-case scenario. Although DP batches are currently being released at low (less than (b) (4)) (b) (4) Free PS, the release specification in place enables Sanofi to release DP batches at (b) (4) Free PS. Therefore, we plotted the (b) (4) Free PS as a function of storage time to uncover trends (Section 3.2.P.8.3, Tables 11, 12, 13 and 14, pages 15, 16, 17 and 18, respectively). The plots followed a linear behavior and were fitted to a straight line to obtain the slope and ordinate values (Figure 8). The slopes obtained represent the MenA (b) (4) during storage ((b) (4) Free PS/month) and were calculated to be between (b) (4) Free MenA(b) (4). This (b) (4) translates to ca. (b) (4) increase in Free MenA over (b) (4) of storage. Considering the available stability data (18 months for commercial (b) (4) DP batches), the calculated (b) (4) from available stability data and the current release and stability specifications of (b) (4) Free PS (b) (4), respectively, DP batches could be out of specification after 36 months of storage at 2°C-8°C. However, to-date, no commercial DP batch has been released (b) (4) Free PS higher than (b) (4). Therefore, the reviewer recommends that the DP (b) (4) shelf-life be set at 36 months, until Sanofi demonstrates that a longer shelf-life is adequate. Setting expiry dating to 36 months will enable Sanofi to introduce available commercial DP batches to the market at a low risk for those batches not conforming to stability specification of (b) (4) Free PS (b) (4). However, if Sanofi releases batches ca. (b) (4) Free MenA, they will most likely fail stability specification at or after 36 months of storage. In such case, the release specification and or shelf-life will have to be re-evaluated.

On 20 March 2020 CBER requested Sanofi to set the (b) (4) DP expiry dating to 36 months at their respective storage condition and provided the rationale for the request. Sanofi responded on

March 27 (STN125701/32). CBER request and a summary of Sanofi's response are provided below.

We have evaluated the data that you submitted in this application (STN 125701/0 for MenQuadfi) to determine a reasonable expiry dating period for your (b) (4) *drug product DP). Our evaluation includes the following to make this decision. In Section 3.2.P.8.3: Stability Data, Tables 11-14, pages 15-18 and in document SWT-REP-021797, Table 29, Page 37,* (b) (4) *Free polysaccharide, you provide stability data for clinical DP batches* (b) (4) *as well as for commercial DP batches* (b) (4) *. By plotting the available* (b) (4) *against the storage time (in months) we derived linear models from which a rate of* (b) (4) *of* (b) (4) *can be projected. At this* (b) (4) *rate,* (b) (4) *can increase between* (b) (4) *during your proposed* (b) (4) *of storage at 2-8 ˚C. A DP batch released at the upper release specification limit of* (b) (4) *, could potentially lead to an out of specification result of greater than* (b) (4) *after 36 months of storage. Since only 18 months of stability data are currently available for commercial* (b) (4) *DP batches, their stability profile over a* (b) (4) *storage period remains uncertain. Therefore, we consider an expiry dating period of no more than 36 months for* (b) (4) *DP batches at their respective storage conditions, to be appropriate. Please set the expiry dating period for* (b) (4) *DP to 36 months in your BLA.*

In response Sanofi updated the following sections of the BLA reflecting the 36 month of expiry dating for (b) (4) DP as well as the corrected (b) (4) stability specification for (b) (4) DP: Sections 3.2.S.7.1 Stability Summary and Conclusions, Section 3.2.S.7.2 Post Approval Stability Protocol and Stability Commitment, Section 3.2.S.7.3 Stability Data for (b) (4) and Section 3.2.P.8.1 Stability Summary and Conclusions, Section 3.2.P.8.2 Post Approval Stability Protocol and Stability Commitment, Section 3.2.P.8.3 Stability Data.

However, Sanofi did not update the (b) (4) DP release specification as proposed on 19 March 2020 (STN 125701/29) and agreed by CBER, via email, on 26 March 2020. Therefore, CBER issued an IR on 31 March 2020. Sanofi responded 02 April 2020 (STN125701/33). CBER questions and a summary of Sanofi's answers are presented below:

Question 1: *You updated the expiry dating for the* (b) (4) *Drug Product (DP) as well as their respective stability specifications, in Section 3.2.S.7 and Section 3.2.P.8 and corresponding subsections. However, you have not yet updated* (b) (4) *DP release specifications (see e.g., Section 3.2.S.4.1, Table 1, page 4, and Section 3.2.P.5.4 Batch Analyses, Table 3, page 10, respectively). Please update the* (b) (4) *DP expiry dating and stability and release specification throughout the submission.*

As requested, Sanofi provided revised documents with the agreed upon (b) (4) release and stability specifications for:

- (b) (4)

- 2.3.P.5Control of Drug Product and subsections 3.2.P.5.1 Specification of Drug Product, 3.2.P.5.4 Batch Analysis of the Drug Product, 3.2.P.5.6 Justification of the Specifications-Drug Product.

Question 2: *In Section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment, page 3, it reads: "The test methods and acceptance criteria for the stability study are* (b) (4) *to those applied at release of the* (b) (4) *unit dose vial with the exception of the container closure integrity test (CCIT) and physical examination." However, the release and stability acceptance criteria of the unit dose vial are no longer the same. Please update the text to reflect the agreed upon acceptance criteria.*

Sanofi updated *Section 3.2.P.8.2* Post Approval Stability Protocol and Stability Commitment to reflect the agreed (b) (4) acceptance criteria.

Sanofi incorporated the changes requested by CBER, therefore Sanofi's responses are adequate.

On 6 April 2020 Sanofi submitted amendment 36 (STN125701/36) providing Section 3.2.P.5.3 Validation of Analytical Procedure-(b) (4) that was not included in Amendment 33 (STN125701/33, 02 April 2020). The provided document contains a summary of (b) (4) validation results already submitted in Amendment 23 (STN125701/23 dated 10 February 2020). (b) (4) validation results are reviewed in pages 201-207 of this memo.

(b) (4) study for Final Container Drug Product (Unlabeled Unit Dose Vial)

Unlabeled and packaged samples were (b) (4) All the QA were comparable between the control, the packed, and the labeled unit dose vials. All conformed to release specifications (Table 19, page 21, Section 3.2.P.8.3).

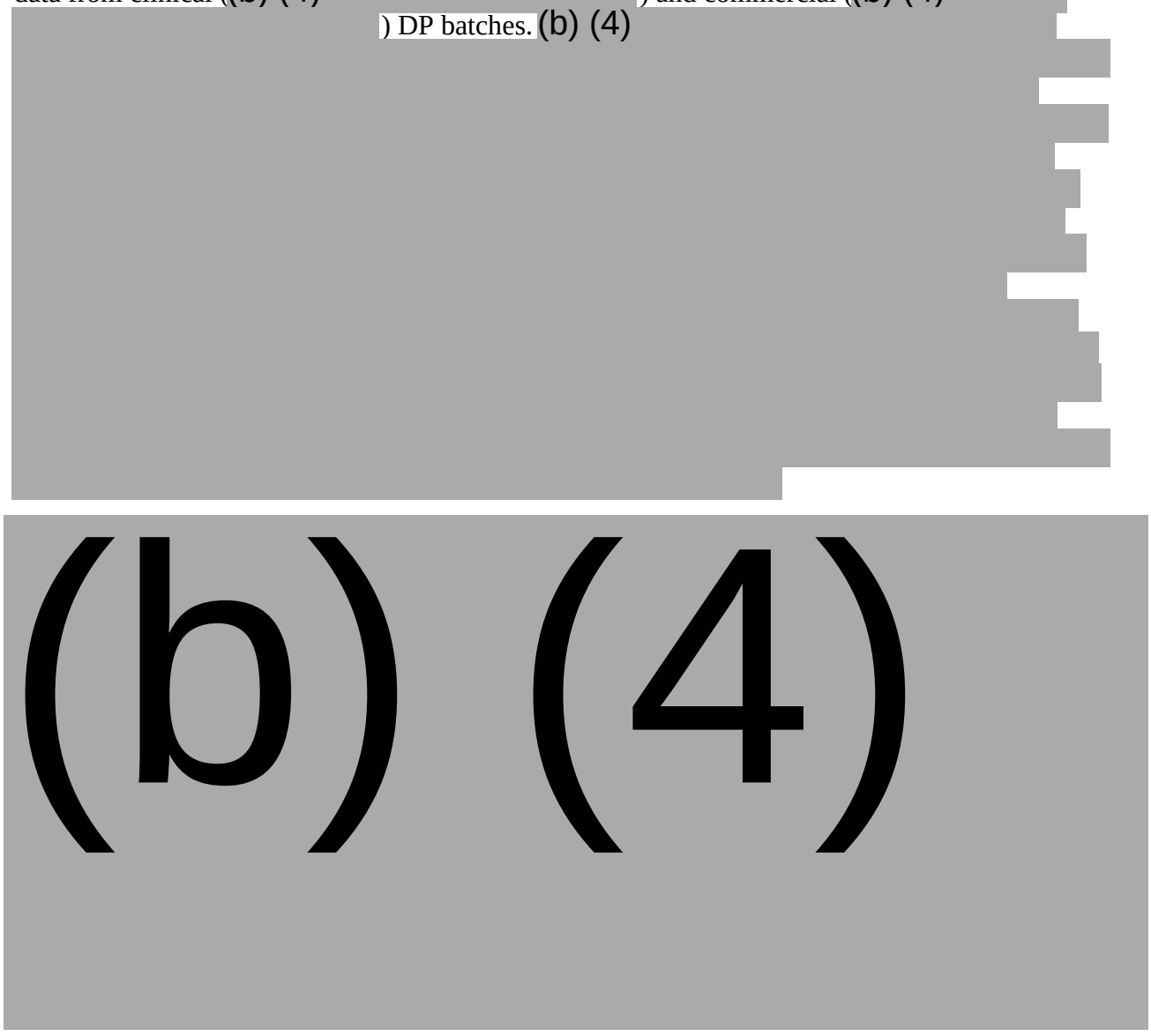
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Sanofi Pasteur commits to completing the on-going studies performed on the DP, Meningococcal (A, C, Y, W135) Polysaccharide TT Conjugate Vaccine Bulk stored under normal storage conditions ((b) (4)) and Unit Dose Vial stored under normal storage conditions (5°C ± 3°C) according to approved stability protocols.

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

The reviewer agrees with Sanofi's commitment.

Figure 8. Rationale for determining DP shelf-life based on available MenA (b) (4) Free PS stability data from clinical ((b) (4)) and commercial ((b) (4)) DP batches. (b) (4)



3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

I defer to DMPQ memo for review of Facilities and Equipment.

3.2.A.2 Adventitious Agents Safety Evaluation

Although ingredients of animal origin are used in the preparation of MENQUADFI, the main theoretical risk of associated with these ingredients is a contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents. Sanofi has worked with its suppliers of raw materials to provide documentation on animal origin information. When possible, animal origin raw materials have been replaced with non-animal origin raw materials. When raw materials from animal origin were used, Sanofi has applied safety and traceability requirements requiring that animal origin raw materials be sourced only from countries classified as geographical BSE Risk (GBR) Level I or II, in compliance with EMEA/410/01. The raw materials from animal origin used in MENQUADI manufacturing process are described and reviewed in pages 12-14 of this document. Certificate of Suitability, Certificate of analysis and supplier source documentation are provided in Section 3.2.S.2.3 Control of Source and Starting Materials of Biological Origin. The documentation provided is adequate.

- **Viral Clearance Studies**

MENQUADFI is a bacterial vaccine, composed from bacterial-derived components. Throughout MENQUADFI manufacturing process, there is no available host for a virus to grow and therefore viral clearance/inactivation is not applicable.

3.2.A.3 Novel Excipients

No non-compendial excipients, no excipients of human or animal origin and no novel excipients are used during manufacture of MENQUADFI.

3.2.R Regional Information (USA)

- **UNII code records**

I reviewed the UNII code designations and found them to be acceptable.

- **Executed Batch Records**

On 26 June 2019, CBER issued an information request letter asking Sanofi to provide the Batch Production Records for DS and DP used in Phase III clinical trials, as well as for the commercial batch. Sanofi responded on 19 July 2019, providing the requested documents. The batch production and filling records (BPR and BFR, respectively) are consistent with the data provided throughout STN 125701/0.

- **Comparability Protocols**

Module 1

In Section 3.2.R Sanofi, provided two comparability protocols with unclear intent. Therefore, CBER issued the following information request letter (IR) to Sanofi dated 24 July 2019:

In 3.2.R (Regional Information) you include Comparability Protocols for Tetanus and Meninge Working Seeds. The purpose of these Comparability Protocols is not clear.

a) Please provide a clear explanation indicating the purpose of the submitted protocols.

b) The content of these comparability protocols is inadequate. Please see Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing and Controls Information Guidance for industry (April 2016) for recommendations for post approval change through the use of a comparability protocol.

As a result, Sanofi requested a teleconference.
CBER and Sanofi held a teleconference on 06 Aug 2019, in which Sanofi acknowledged the lack of clarity of the provided documents explaining that the comparability protocols in questions were already approved for (b) (4) , vaccines for which the same bacterial seeds as for MENQUADFI are used. CBER acknowledged Sanofi's response and requested Sanofi to submit their formal answers for review. Sanofi's answers were received 23 August 2019 (STN 125701/6), providing references to the approved comparability protocols, as well as the clarification that the comparability protocols provided as part of the MENQUADFI BLA are identical to the previously approved comparability protocols with respect to the technical content. Moreover, Sanofi explained that the purpose of the comparability protocols is to reduce the reporting category for the use of new working seed banks from a prior approval supplement (PAS) to an Annual Report (AR). Sanofi's answers are adequate and were agreed upon during 06 August 2019 teleconference with CBER.

A. Environmental Assessment or Claim of Categorical Exclusion

Sanofi states that STN125701 qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(c) which states that the environmental assessment can be excluded for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

B. Labeling Review

Full Prescribing Information (PI):
I reviewed and provided comments on the proposed labeling for MenQuadfi (container label, carton, and package insert).

Modules 4 and 5
Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

5. CLINICAL STUDY REPORTS

9.2. Tabular Listing

Sanofi provided a table detailing the five pivotal clinical studies (MET35, MET43, MET49, MET50, and MET56) and three supportive studies (MET28, MET32, and MET44) that support the proposed indication for MENQUADFI. See Clinical Review memorandum for additional information regarding individual study objectives and design.

9.2.1. Reports of Biopharmaceutic Studies

Submitted document "Immunological Assay Methods" provided an introduction to the immunological assays that were utilized in the clinical studies to determine comparability 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, MenY, and MenW responses to meningococcal vaccines was the human complement serum bactericidal assay (hSBA); (b) (4) was used in supportive studies. Additional assays included the Diphtheria Toxin Neutralization Assay (TNA (b) (4)), the Tetanus (b) (4) ELISA, and four Pertussis (b) (4) ELISAs to measure responses to the Tdap (ADACEL®) vaccine. This review will focus only on the serological data submitted to assess immunogenicity in the Phase II and Phase III pivotal studies.

Validation of Immunogenicity Assays

Meningococcal hSBA. In the hSBA, (b) (4)

A validation study was performed for each of the meningococcal hSBAs using the following strains: MenA, (b) (4); MenC, (b) (4); MenY, (b) (4); MenW, (b) (4) (C009076, Report for Protocol B007294, "Protocol for Serum Bactericidal Assay for the Detection of Meningococcal Antibodies Using Human Complement"). The validation study assessed precision, accuracy, dilutability, specificity, and stability for each of the assays, and defined the range and the Upper (ULOQ) and Lower Limits of Quantitation (LLOQ). For all serogroups, the hSBA data demonstrated sufficient precision, accuracy, dilutability, and stability. However, the positive control serum sample in the specificity assays was not inhibited by (b) (4) derived from any of the meningococcal serogroups and was replaced with an alternate control in all subsequent validation studies. Additionally, the LLOQ was not adequately supported due to lack of sufficient data.

To determine the LLOQ, additional samples targeting the lower range of the assays were tested against each of the four strains. Reports of those supplemental analyses were provided in the following documents: C010064, Validation Report for Serogroup A SBA-HC Titers of 1:4, 1:8 and 1:16 Measured by SWI J001680, "Serum Bactericidal Assay for the Detection of Meningococcal Antibodies Using Human Complement", C010065, Validation Report for Serogroup C SBA-HC Titers of 1:4, 1:8 and 1:16 Measured by SWI J001680, "Serum Bactericidal Assay for the Detection of Meningococcal Antibodies Using Human Complement", C010067, Validation Report for Serogroup Y SBA-HC Titers of 1:4, 1:8 and 1:16 Measured by SWI J001680, "Serum Bactericidal Assay for the Detection of Meningococcal Antibodies Using Human Complement", and C010066, Validation Report for Serogroup W135 SBA-HC Titers of 1:4, 1:8 and 1:16 Measured by SWI J001680, "Serum Bactericidal Assay for the Detection of Meningococcal Antibodies Using Human Complement". The repeat analyses demonstrated sufficient accuracy and precision at the lower range of the assay and the LLOQ for each of the assays was defined as a titer of 1:4. The additional studies were considered adequate to support the LLOQ (see memo from Freyja Williams to IND 14171, Amendment 98).

Diphtheria TNA. Associated documentation for the TNA has been provided under 125701.0, Section 5.3.1.4, Inter Laboratory Standardization Methods Quality Assurance:

GDMS_568394 – Determination of Corynebacterium diphtheriae Toxin Functional Antibodies by Toxin Neutralization Assay, Version 3.0
Q_0293450 – Validation Report for SOP #37S2, "(b) (4) for Diphtheria Antitoxin", V04-433A-01, dated 9 October 1997
Q_0521174 – Validation Report for Instruction Q_0277558, "Determination of Corynebacterium diphtheriae Toxin Functional Antibodies by Toxin Neutralization Assay", Version 1.0
Q_0250204 – Transfer Report for B000806 Transfer of SOP #A00837 "Determination of Diphtheria Antitoxin in International Units" from Clinical Serology Bldg. (b) (4) to Clinical Serology Bldg. (b) (4), Version 1.0

The diphtheria TNA assay is an *in vitro* functional assay that measures levels of diphtheria toxin neutralizing antibodies in human sera. (b) (4)

The diphtheria TNA performed by (b) (4) was reviewed under IND 14171, Amendment 31 (29 November 2012, see memo dated 24 July 2013 by Leslie Wagner and Freyja Lynn). The agency conveyed comments to the sponsor regarding the use of the (b) (4) assay. While some aspects of the method and validation were not consistent with current best practices applied to assays developed more recently, CBER recognized that this assay has been used to support previous licensing actions and saw no immediate need for updating the assay or validation. Sanofi submitted Amendment 50 under IND 14171, acknowledging CBER's comments. The diphtheria TNA assay was determined to be acceptable for its intended use in clinical study MET50.

Tetanus (b) (4) ELISA. Associated documentation for the Tetanus (b) (4) ELISA was provided under 125701.0, Section 5.3.1.4, Inter Laboratory Standardization Methods Quality Assurance:

GDMS_546826 – ELISA Method for the Determination of Tetanus Antibodies in International Units, Version 15.0
Q_0249865 – Validation Report for J0000051, "Elisa Method for the Determination of Tetanus Antibodies in International Units: C000149-02
Q_0250234 – Transfer Validation Report for SWI J000051 "ELISA Method for the Determination of Tetanus Antibodies in International Units" from Bldg. (b) (4) to Bldg. (b) (4), Version 1.0

The tetanus (b) (4) ELISA is an enzyme-linked immunosorbent assay that uses (b) (4)

The tetanus (b) (4) ELISA performed by (b) (4) was reviewed under IND 14171 Amendment 31 (26 November 2012, see memo dated 24 July 2013 by Leslie Wagner and Freyja Lynn). The assay was validated in 2003 and consistent long-term performance has been observed from November

2001 to July 2012. The tetanus (b) (4) ELISA was determined to be suitable for measuring anti-tetanus antibody responses.

Pertussis (b) (4) ELISAs. Associated documentation for the Pertussis (b) (4) ELISAs was provided under BLA 125701.0, Section 5.3.1.4, Inter Laboratory Standardisation Methods Quality Assurance:

GDMS_538185 – ELISA Method for the Detection of Human Antibodies to PT Antigen, Version 3.0
Q_0254868 – Validation Report for SWI J003829, "ELISA Method for the Detection of Human Antibodies to Pertussis Toxin (PT) Antigen" C008666, Version 4.0
GDMB_511393 – ELISA Method for the Detection of Human Antibodies to Filamentous Haemagglutinin Antigen, Version 2.0
Q_0254615 – Validation Report for SWI J003792, "ELISA Method for the Detection of Human Antibodies to Filamentous Haemagglutinin" C008396, Version 2.0
GDMS_549400 – ELISA Method for the Detection of Human Antibodies to Fimbrial Agglutinogens (2+3) Antigens, Version 2.0
Q_0254614 – Validation Report for SWI J003847, "ELISA Method for the Detection of Human Antibodies to Fimbrial Agglutinogens (2+3) Antigen C008395, Version 2.0
GDMS_500694 – ELISA Method for the Detection of Human Antibodies to Pertactin ((b) (4)) Antigen, Version 3.0
Q_0254611 – Validation Report for SWI J003848, "ELISA Method for the Detection of Human Antibodies to Pertactin ((b) (4)) Antigen" C008392, Version 2.0

The Pertussis (b) (4) ELISAs follow a similar principle to the Tetanus (b) (4) ELISA. However, (b) (4) are tested using this process; (b) (4)

The pertussis (b) (4) ELISAs performed by (b) (4) were reviewed under IND 14171, Amendment 49 (26 November 2013). The ELISAs were also reviewed under IND 14688 and BLA 125563/0 (see memo from Freyja Lynn to 125563/0 dated 9 December 2014). The assays were deemed acceptable for the intended use in clinical study MET50.

Demonstration of Stability of Serological Assays. Sanofi provided the document GDMS_596840 "Demonstration of the Long-Term Performance of the Diphtheria TNA, Tetanus ELISA, Pertussis ELISA and hSBA for MenQuad-TT", which described the assay reference standard and Internal Quality Control (IQC) results generated as part of clinical and non-clinical

testing encompassing the time in which serology testing was performed for the MENQUADFI clinical studies.

For the meningococcal hSBAs, Internal Quality Controls (IQCs) were run throughout the performance of serology testing for the clinical studies (March 2011 – October 2017) to assess any observational trends indicative of changes in assay stability. Initially, (b) (4) control (IQC1) was utilized for testing of all four serogroups during MET44, with acceptance limits ranging from titers of (b) (4), depending on the serogroup. IQC2 (acceptance limits of (b) (4), depending on serogroup) and IQC3 (acceptance limit of (b) (4)) were introduced in March 2014, during testing of MET50 and MET56 samples; ICQ3 was removed in October 2016. Occasionally, datasets fell outside of acceptable limits, but no apparent change in assay stability was observed throughout the testing period for any of the serogroups, despite introduction of new IQCs. The data supported the stability of the hSBAs throughout the time period from assay validation to clinical testing.

For the Diphtheria TNA assay, trending for the assay reference standard and IQC were examined. An assay low positive control (IQC2) and an assay negative control (IQC3) were introduced in 2014. Data for the period extending from May 2014 to September 2017 were provided. The data support the stability of the assays during its use in the MET50 study, performed March 2015 – May 2015.

For the Tetanus (b) (4) ELISA, (b) (4) control of the assay of over time were examined. (b) (4) were presented for each day the ELISA was run. The data support the stability of the assay during its use in the MET50 study, performed January 2015 – August 2015.

For the Pertussis (b) (4) ELISAs, data for the (b) (4) control for the anti-PT, anti-FHA, anti-FIM 2+3, and anti-PRN (b) (4) ELISAs over time were plotted. The (b) (4) were presented for each day for the days which clinical testing was performed (April 2015 – July 2015). The data supported the stability of the assays during its use in the MET50 study.

Clinical Study Reports

The immunogenicity data from the following study reports were reviewed to confirm that the data support the study conclusions. The immunogenicity data and conclusions from each study were also reviewed under the IND; see reference to the relevant review memos below. See clinical reviewer memo for full descriptions and review of each study. The summary of the results from each study are included below.

MET35: Immunogenicity and Safety of an investigational Quadrivalent Meningococcal Conjugate Vaccine Administered in Healthy Children 2 to 9 Years of Age (see memo from Freyja Williams to IND 14171, Amendment 133)

The results showed that the responses against all serogroups were higher in the subjects who received MENQUADFI than those who received MENVEO. For MenA, MenC, MenY, and MenW, the percentage of subjects with an hSBA vaccine seroresponse in Group 1 was 55.4% (252/455), 95.2% (436/458), 91.5% (419/458), and 78.8% (361/458), respectively; responses for the equivalent serogroups in Group 2 were 47.8% (219/458), 47.8% (219/458), 79.3% (364/459), and 64.1% (294/459), respectively. The lower limits of the 2-sided 95% confidence intervals (CIs) were above -10% for all serogroups. The GMTs at Day 30 through Day44 (D30-D44) were consistent with the seroresponse results, with the lower limits of the 2-sided 95% CIs of the geometric mean titer ratios (GMTRs) all >1.0. No unusual or aberrant data were seen in the results.

MET43: Immune Lot Consistency, Immunogenicity, and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults Aged 10 to 55 Years (see memo from Freyja Williams to IND 14171, Amendment 133)

The clinical criterion for lot consistency was met. The 2-sided 95% CIs of the ratios of the GMTs were between >0.5 and <2 for each pair of lots and each serogroup. In addition, non-inferiority of immune response was demonstrated between MENQUADFI and MENACTRA based on percentage of subjects achieving hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was >-10%. The percentage of subjects with an hSBA vaccine seroresponse was numerically higher in Groups 1-3 (pooled) relative to Group 4 for all serogroups, ranging from 73.8% (1846/2503) to 91.4% (2290/2505) in Groups 1-3 and from 47.9% (284/593) to 73.4% (435/593) in Group 4.

The reverse cumulative distribution curves (RCDCs) were consistent with the seroresponse and GMT data, with the curves for subjects who received MENQUADFI shifted to the right when compared with the curves for subjects who received MENACTRA. No unusual or aberrant data were seen in the results.

MET49: Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adults Age 56 Years and Older (see memo from Freyja Williams to IND 14171, Amendment 134)

The criteria for noninferiority of responses to MENQUADI when compared to MENOMUNE were met. The responses to MENQUADI were higher than the responses to MENOMUNE for all serogroups. The differences ranged from 15.7% to 31.0%, with the response rates against the meningococcal serogroups defined as the following:

- Group 1: MenA, 58.2% (252/433); MenC, 77.1% (334/433); MenY, 74.4% (322/433); MenW, 62.6% (271/433)
- Group 2: MenA, 42.5% (183/431); MenC, 49.7% (214/431); MenY, 43.4% (187/431); MenW, 44.8% (193/431)

The response rates against serogroups Y and W for subjects who received MENQUADI were lower in subjects ≥75 years old when compared to those 56-64 years old, but remained higher than in subjects of the same ages who received MENOMUNE. The GMT data and RCDC data were consistent with the seroresponse data. No unusual or aberrant data were seen in the results.

MET50: A Phase II Study of the Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Healthy Adolescents (see memo from Freyja Williams to IND 14171, Amendment 134)

Sanofi provided the clinical study report for MET50 to evaluate the concomitant administration of MENQUADI with licensed vaccines, Tdap and HPV (GARDASIL®). The report, provided under section 5.3.5.1 met50, was reviewed by Freyja Williams under IND 14171, Amendment 95. The primary objective of the study was to evaluate and compare the MenA, MenC, MenY, and MenW antibody responses to MENQUADI and MENVEO. The secondary objective related to the evaluation of responses to the meningococcal serogroups or to the Tdap vaccine when the vaccines were administered concomitantly or were given alone (or with the HPV vaccine, in the case of Tdap). Subjects were randomized into one of four groups as shown below:

Group 1 – MENQUADI alone
Group 2 – MENVEO alone
Group 3 – MENQUADI, Tdap, and HPV vaccines
Group 4 – Tdap and HPV vaccines

The hSBA responses to each of the groups were tested separately. If the lower limit of the 2-sided 95% CI of the difference between the proportions was >-10%, the inferiority assumption was rejected. hSBA vaccine seroresponse for the meningococcal serogroups was defined as post-vaccination titers ≥1:8 for subjects with baseline titers <1:8 or a ≥4-fold increase in hSBA titers for post-vaccination samples relative to baseline for subjects with baseline titers ≥1:8. The noninferiority criteria for the comparison between responses against MENQUADI versus those against MENVEO were met. The differences ranged from 9.2% to 24.6%, with the response rates against the meningococcal serogroups defined as the following:

- Group 1: MenA, 75.6% (350/463); MenC, 97.2% (449/462); MenY, 97.0% (448/462); MenW, 86.2% (399/463)
- Group 2: MenA, 66.4% (308/464); MenC, 72.6% (336/463); MenY, 80.8% (375/464); MenW, 66.6% (309/464)

The secondary meningococcal objective compared the seroresponse rates against MENQUADI administered alone or concomitantly with Tdap and HPV. The differences ranged from -1.4% to 5.0%, with the seroresponse rates against the meningococcal serogroups in Group 3 defined as the following: MenA, 80.6% (390/360); MenC, 97.2% (350/360); MenY, 95.6% (344/360); MenW, 83.9% (302/360). The GMT data and RCDC data were consistent with the seroresponse data.

For measurement of Tdap responses, the criterion for noninferiority was that the lower 95% CI of the ratio of the antibody responses of Group 3 versus Groups that received respective MENQUADI (Group 1) or Tdap/HPV vaccines (Group 4) alone had to be more than 2/3 (0.667) measured at D30 post-vaccination. Noninferiority was met for responses against tetanus, diphtheria, and the PT antigen, but not the responses against FHA, PRN, and FIM antigens. The lower 95% CI for FHA and PRN were close to the cut-off (0.661 and 0.627, respectively) while the lower limit for FIM was 0.525. In her review of MET50, Freyja Williams noted that concomitant administration of MENQUADI with Tdap resulted in lower responses to all of the pertussis antigens when compared to the responses when the vaccines were administered separately. The RCDCs indicated that the lower GMTs to FHA, PRN, and FIM in the concomitantly-administered group were due primarily to differences at the high end of the range of titers. Thus, although the GMTs were lower in the group that received vaccines concomitantly, the differences were unlikely to be clinically significant. However, the RCDCs showing the responses to PT indicated that the curves for the two groups began to diverge at a titer less than or equal to 10 EU/mL. The maximum divergence appeared to be less than 10%, but the clinical relevance of an increased number of subjects with lower antibody levels could not be determined. The clinical reviewer will need to determine if the data are sufficient for a labeling claim for concomitant administration of Tdap with MENQUADI.

For all studies, no unusual or aberrant data were noted during review.

MET56: Immunogenicity and Safety of a Booster Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults (see memo from Freyja Williams to IND 14171, Amendment 131)

The primary objective was to demonstrate the non-inferiority of the vaccine seroresponse to MenA, MenC, MenY, and MenW following the administration of a booster dose of MENQUADI (Group 1) vs. MENACTRA (Group 2) in subjects administered a primary vaccination of either MENACTRA or MENVEO 4-10 years prior. The seroresponse rate at D30-D44 post-vaccination for MENQUADI-vaccinated subjects met the non-inferiority criteria when compared to the subjects who received MENACTRA. The results of the data analyses for the D30-D44 post-vaccination per-protocol analysis set 2 (PPAS2) subset of subjects were consistent across the secondary and observational endpoints.

The report also included an analysis of responses stratified by the primary conjugate vaccine received, either MENVEO, MENACTRA, or unknown. Of the 384 subjects in Group 1, 327 had received MENACTRA previously, 48 had received MENVEO, and nine had received an unknown vaccine. The relative numbers in Group 2 were similar, a total of 389 subjects with 340, 39, and 10 having received MENACTRA, MENVEO, or an unknown vaccine, respectively. While the number of subjects who received MENVEO was small, the data suggest no meaningful difference between the responses to MENQUADI for subjects who had received MENACTRA or MENVEO as their primary dose.

The data tables did not compare the D30-D44 post-vaccination seroresponses between the two per-protocol populations. However, the RCDCs included the data from D30-D44 for both per-protocol group. The curves were consistent across the two per-protocol subsets of subjects for responses against MenA and MenY. In addition, the curves of the responses to MenC in Group 2 and to MenW in Group 1 were consistent. The curve of responses in PPAS2 against MenC in Group 1, however, were substantially shifted when compared to the curve of the D06 post-vaccination responses in PPAS1, with the overall responses in PPAS2 up to 4-fold higher. The curve of responses in PPAS1 against MenW in Group 2 was also substantially shifted when compared to the curve of the responses in PPAS2, with the responses in PPAS1 up to 4-fold higher. Upon communication by CBER regarding the necessity for submission of an analysis to demonstrate the two per-protocol sets of data were unbiased (see e-mail correspondence from Joseph Temenak dated 16 November 2018), SP clarified in IND 14171, Amendment 147 that a comparison of the D30-D44 responses between PPAS1 and PPAS2 was not pre-specified as an endpoint for the clinical trial and MET56 was not designed to compare the respective subsets. The response was deemed adequate (see Freyja Williams' memo dated 28 March 2019).

No unusual or aberrant data were seen in the results.