CBER DMPQ CMC BLA Review Memorandum

BLA STN 125701/0

MenQuadfi™ [Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine]

Gregory Price/Biologist/DMPQ

U.S. FOOD & DRUG ADMINISTRATION

1. BLA#: STN 125701/0

2. APPPLICANT NAME AND LICENSE NUMBER
Sanofi Pasteur Inc., License #1725

3. PRODUCT NAME/PRODUCT TYPE
MenQuadfi™/Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmacological category
Vaccine

b. Dosage form
Sterile solution for injection supplied in unit dose vials

c. Strength/Potency
The formulation contains four drug substances comprised of serogroup-specific polysaccharide antigens purified from Neisseria meningitidis Serogroups A, C, Y, and W135, separately conjugated to tetanus toxoid.
The target formulated concentration per dose (0.5 mL) is:

Component	Formulated Quantity (0.5 mL dose)	Function
Meningococcal (Serogroup A) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Meningococcal (Serogroup C) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Meningococcal (Serogroup Y) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Meningococcal (Serogroup W135) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient
Tetanus Toxoid, Filtered Concentrate	55 µg*	Carrier Protein

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

d. Route of administration
Intramuscular injection

e. Indication(s)
The target indication is active primary and booster immunization for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y in individuals 2 years of age and older.

5. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
4/26/2019	STN 125701/0	Main submission. Reviewed
5/28/2019	STN 125701/0.1	ANDA Basis for Submission Statement. Reviewed
7/19/2019	STN 125701/0.4 (response to IR #1)	Clarification regarding (b) (4) equipment and building usage. Also, concurrent IR from PO regarding missing batch records in original submission. Responses were adequate.
8/23/2019	STN 125701/0.6	Updated DP stability data
11/22/2019	STN 125701/0.17 (response to IR #2)	IQ/OQ and CVs for new equipment in (b) (4)
3/25/2020	STN 125701/0.31 (response to IR #3)	Results from most recent media fill challenge and inspection results from MenQuadfi DP batches

6. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

MenQuadfi is a new meningococcal polysaccharide tetanus toxoid conjugate vaccine which is manufactured from the currently licensed FDA component drug substances listed below:

- The *N. meningitidis* seed banks and polysaccharide purified bulk (b) (4) (Serogroups A, C, Y and W135) are currently used in (b) (4) .
- The Tetanus seed banks, Purified and Concentrated Tetanus Protein are currently used in (b) (4) .

All manufacturing and testing of bacterial seeds, drug substance intermediates, drug substances and drug product occur in existing licensed facilities at both the Sanofi (b) (4) and Swiftwater, PA sites which are currently utilized for commercial production. The manufacturing

processes for both the drug substances and final drug product did not require any facility or utility changes to accommodate the production of MenQuadfi.

MenQuadfi and the currently approved meningococcal conjugate vaccine, (b) (4) , contain similar processing steps except for (b) (4) utilized for MenQuadfi. All manufacturing steps to produce MenQuadfi have been validated in the current submission.

B. RECOMMENDATION

I. APPROVAL

Based on the information provided in this application, approval is recommended.

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Gregory Price, Biologist, DMPQ BI	Concur	
Lori Peters, Acting Branch Chief, DMPQ BI	Concur	
John A. Eltermann, Jr, Director, DMPQ	Concur	

Review of CTD
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Module 3

3.2.S DRUG SUBSTANCE

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

We defer review of this section to the product office.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The manufacturers names addresses are provided in the Table below:

Name and Address of the Manufacturers

Sanofi Pasteur Site	Address
Sanofi Pasteur ((b) (4))	(b) (4) FDA Registration Number: (b) (4)
Sanofi Pasteur, Inc. (SWT)	Discovery Drive Swiftwater, PA 18370- 0187 USA FDA Registration Number: 1725

From here forward, the Swiftwater and (b) (4) sites will be abbreviation as SWT and (b) (4), respectively. The tetanus toxoid manufacturing that occurs at (b) (4) includes the following steps:

- Propagation and fermentation of *Clostridium tetani* which occurs in Building (b) (4).
- Tetanus toxin purification and detoxification which also occurs in Building (b) (4).
- Concentration and filtration of tetanus toxoid (Henceforth abbreviated as TT) which occurs in Building (b) (4).

At (b) (4) the release and stability testing of the *Clostridium tetani* seeds and purified/concentrated tetanus toxoid is conducted in Building (b) (4).

SWT conducts the following manufacturing operations occur:

- Propagation and fermentation of the *N. meningitidis* Seed stocks (Serogroups A, C, W, and Y)
- Filtration of the concentrated TT.
- Purification of *N. meningitidis* Polysaccharide (b) (4), Serogroups A, C, W, and Y.
- Activation/Derivatization of *N. meningitidis* Polysaccharide Concentrates, Serogroups A, C, W, and Y.
- *N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrates, Serogroups A, C, W, and Y.

SWT conducts the following release/stability testing:

(b) (4)

It should be noted that the manufacture of both the meningococcal polysaccharides and tetanus toxoid are previously approved processes used in the production of the FDA approved vaccines (b) (4)

3.2.S.2.2 Description of Manufacturing Process

The manufacture of the Drug Substances, *N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrates Serogroups A, C, Y and W135 consists of the following major manufacturing process stages:

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT[1]

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

The drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, is a unit dose liquid presentation for intramuscular use. The formulation contains four drug substances comprised of serogroup-specific polysaccharide antigens purified from *Neisseria meningitidis* Serogroups A, C, Y, and W135, separately conjugated to tetanus toxoid. The drug product vaccine formulation is prepared as a sterile, aqueous solution containing sodium acetate and sodium chloride buffers. The physical appearance description of the vaccine formulation is listed in the table below.

Physical Appearance of Drug Product - Meningococcal Polysaccharide (Serogroups A, C, Y and W135) Tetanus Toxoid Conjugate Vaccine

Formulation	Physical Appearance
Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine	Clear solution

The target formulated concentration and function of each of the components contained within the drug product is described in the table below.

Composition of the Final Container Drug Product - Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Component	Formulated Quantity (0.5 mL Dose)	Function	Reference to Quality Standards
Meningococcal (Serogroup A) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient	In-house
Meningococcal (Serogroup C) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient	In-house
Meningococcal (Serogroup Y) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient	In-house
Meningococcal (Serogroup W135) Polysaccharide (Monovalent Conjugate)	10 µg	Active Ingredient	In-house
Tetanus Toxoid, Filtered Concentrate	55 µg*	Carrier Protein	In-house
Sodium Chloride within (b) (4) Sodium Chloride Solution)	3.35 mg (0.67%)	Excipient used to (b) (4)	(b) (4)
Sodium Acetate (within (b) (4) Sodium Acetate, (b) (4) Solution)	1.23 mg (30mM)	Excipient used to (b) (4)	(b) (4)

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

The vaccine is supplied in a 2 mL unit dose vial. The 2 mL vial is 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). The filled vial with stopper is sealed with a 13 mm aluminum seal with plastic flip cap.

3.2.P.2 Pharmaceutical Development
3.2.P.2.1 Components of the Drug Product
3.2.P.2.1.1 Drug Substance
N. meningitidis Polysaccharide Tetanus Toxoid Conjugate Concentrate, Serogroups A, C, Y and W135 are the four drug substances used to formulate the drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine.

***N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrate, Serogroup A**

(b) (4)

***N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrate, Serogroup C**

(b) (4)

***N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrate, Serogroups Y and W135**

(b) (4)

(b) (4)

Active Substances

The target formulated concentration of each active substance contained within a 0.5 mL dose of vaccine and its function is described in the table below.

Active Substances in the Drug Product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Component	Formulated Quantity (0.5 mL dose)	Function
Meningococcal (Serogroup A) Polysaccharide (Monovalent Conjugate)	10 μg	Active Ingredient
Meningococcal (Serogroup C) Polysaccharide (Monovalent Conjugate)	10 μg	Active Ingredient
Meningococcal (Serogroup Y) Polysaccharide (Monovalent Conjugate)	10 μg	Active Ingredient
Meningococcal (Serogroup W135) Polysaccharide (Monovalent Conjugate)	10 μg	Active Ingredient
Tetanus Toxoid, Filtered Concentrate	55 μg*	Carrier Protein

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

Buffer Solutions

(b) (4) sodium chloride is added to maintain the (b) (4) of the vaccine. Sodium chloride was selected due to its prevalent use in many commercial vaccines. (b) (4) sodium acetate, (b) (4) is added to maintain a (b) (4) in the vaccine. (b) (4) sodium acetate, (b) (4) was selected based on its (b) (4) buffering capability.

3.2.P.2.1.2 Excipients

The excipients used in the drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine are sodium chloride (within (b) (4) Sodium Chloride Buffer Solution) and sodium acetate (within (b) (4) Sodium Acetate, (b) (4) Buffer Solution). The target formulated concentration of each excipient contained within a 0.5 mL dose of vaccine and its function is described in the table below.

Excipients in the Drug Product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Component	Formulated Quantity (0.5 mL dose)	Function
Sodium Chloride (within (b) (4) Sodium Chloride Solution)	3.35 mg (0.67%)	Excipient used to (b) (4)
Sodium Acetate (within (b) (4) Sodium Acetate, (b) (4) Solution)	1.23 mg (30mM)	Excipient used to (b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

We defer review of this section to the PO.

3.2.P.2.2.2 Overages

We defer review of this section to the PO.

3.2.P.2.2.3 Physicochemical and Biological Properties

We defer review of this section to the PO.

3.2.P.2.3 Manufacturing Process Development

We defer review of this section to the PO.

3.2.P.2.4 Container Closure System

The Meningococcal (Serogroups A, C, Y, and W135) Polysaccharide Tetanus Toxoid Conjugate Vaccine is filled in Type I borosilicate 2 ml glass vials, closed with a 13 mm gray (latex free butyl rubber) stopper and a 13 mm flip-off seal. This container closure system is a standard configuration within Sanofi Pasteur.

The components of the container closure system, with a justification for the choice of each component in direct contact with the product, are provided below:

- Type I borosilicate glass vial: this vial has an (b) (4) treated surface and complies with the (b) (4) USP. Type I glass is generally accepted as being inert and therefore the most suitable material to be in contact with preparations for parenteral use.
- Gray chlorobutyl synthetic polyisoprene blend (latex free) rubber stopper: the stopper surface is treated with (b) (4) and is compliant with both (b) (4)

This container closure system has been in use throughout the development of the Drug Product, with the only difference being the vial capacity.
A (b)(4) ml USP Type 1 glass vial was used in the Phase 1 and Phase II clinical trials. The 2 ml vial was used in the Phase IIB and Phase III clinical trials and will be licensed for use with the Drug Product.

Compatibility with the Meningococcal (Serogroups A, C, Y, and W135) Polysaccharide Tetanus Toxoid Conjugate Vaccine, vial and stopper was demonstrated through:

- Extractable/Leachable studies;
- Cytotoxicity studies; and
- Stability studies

For the purposes of this review I will defer the review of the extractable/leachable and cytotoxicity studies to the PO.

Development Stability Studies
The Meningococcal (A, C, Y, and W135) Polysaccharide Tetanus Toxoid Conjugate Vaccine, Unit Dose Vial has been included in the stability program in order to evaluate its 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 ascertain the compatibility of the components with the Drug Product verifying that no interaction had occurred causing an unacceptable change in the quality of Drug Product or container/closure system.

Real time stability studies generated data to support the projected shelf life of (b) (4) at 2°C to 8°C for the unit dose final container when stored in (b)(4) ml glass vials that were used during the Phase II study and tested through (b) (4) at 2°C to 8°C for the one (1) Phase II batch produced in 2014.

Real time stability studies will also generate data to support the projected shelf life when stored in 2 ml glass vials, with a 13 mm, butyl latex free serum stopper and a 13 mm seal with a flip-off seal. The 2 ml vials used during the Phase IIb and Phase III studies are being tested through (b) (4) at 2°C to 8°C for the batches produced in 2014 and 2015, respectively. The (b)(4) ml glass vials used during the Phase II study are currently being tested through (b) (4) at 2°C to 8°C for the one (1) Phase II batch produced in 2014. There have been no changes to the formulation since the Phase II studies and therefore the stability studies from Phase II onwards can be considered as supportive for the current process validation and comparability studies currently ongoing. The duration of each of these studies was selected to cover or exceed the (b) (4) shelf life for the Drug Product.

Sterility and container closure integrity were tested for these various clinical lots with no issues of loss of sterility or container closure integrity. The data collected supports the (b) (4) shelf life at 2°C to 8°C in 2 mL unit dose vials made of Type I USP borosilicate glass, a 13 mm, gray chlorobutyl synthetic polyisoprene blend (latex free) stopper, and a 13 mm flip-off seal. In addition, the container closure system selected for the final container vaccine is considered to be compatible with the Drug Product.

3.2.P.2.5 Microbiological Attributes

The Drug Product Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine formulated and filled in Building (b) (4) at the Swiftwater, PA facility has never contained any preservatives and possesses no inherent antimicrobial properties. Microbiological control is maintained during the manufacturing process, employing sterile filtration, aseptic filling processes, equipment cleaning and sterilization, clean facility design and environmental monitoring.

The bulk is formulated to final vaccine strength and then sterile filtered through a (b) (4) filter into the (b) (4). The final bulk is then aseptically filled into unit dose vials. The filling process also includes an (b) (4) step at (b) (4). During manufacturing, controls are in place to ensure sterility of the final bulk and 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 ability of the formulation bulk (b) (4) and the final container closure system to prevent microbial contamination has been verified through integrity testing studies.

Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, Bulk

Container Closure Integrity

(b) (4)

(b) (4)

(b) (4)

Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, Unit Dose Vials

Container Closure and Package Integrity

The container closure system for the Filled Drug Product is comprised of 2 mL vials made of United States Pharmacopoeia (USP) Type 1 borosilicate glass, with a 13 mm gray (latex free butyl rubber) stopper and a 13 mm seal with a flip-off button. The container closure system for the 2 mL vial is described above. A (b) (4) mL vial was used for the Phase I and Phase II clinical trial material.

Stability studies for clinical trial material as well as process validation batches have been conducted. The studies, performed at actual storage conditions (2°C to 8°C) and accelerated storage conditions of (b) (4), demonstrate the ability of the container closure system to remain integral and maintain product sterility over the proposed shelf life of (b) (4).

Container Closure Integrity Testing (CCIT) for the 2 mL vial

The CCIT study for the 2 mL unit dose vial presentation was successfully performed. All samples were tested using a (b) (4) challenge and a (b) (4) for analysis. The CCIT evaluation was conducted as part of the process validation lots of the component system and the final container routine stability study.

(b) (4)

The validation demonstrated that the samples pass the (b) (4) container closure challenge and maintain unit integrity under (b) (4) conditions.

The implemented facility and manufacturing controls (storage of (b) (4) , aseptic filling operations, and environmental monitoring) have been demonstrated to be adequate through the media hold, CCIT, and stability testing. These controls are suitable to ensure integrity and sterility of the final DP.

3.2.P.2.6 Compatibility

The Meningococcal Polysaccharide (Serogroups A, C, Y and W135) Tetanus Toxoid Conjugate Vaccine is a ready-to use formulation; therefore, there is no reconstitution or dilution of the

Meningococcal Polysaccharide (Serogroups A, C, Y and W135) Tetanus Toxoid Conjugate Vaccine or administration with other dosage devices.

Overall Reviewer's Assessment of Section 3.2.P.2:

- The data provided here is adequate. There were no problems associated with microbiological control of bulk or final DP. The final unit vials have been shown to maintain sterility and integrity up to at least (b) (4) . No additional inquires required here.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Name and Address of the Manufacturer and Testing Sites

Sanofi Pasteur Site	Address
Sanofi Pasteur, Inc.	Discovery Drive Swiftwater, PA 18370 USA FDA Registration Number: 1725
Sanofi Pasteur (b) (4)	(b) (4) FDA Registration Number: (b) (4)

Sanofi Pasteur, Inc. has licenses to manufacture, test, store, and distribute vaccines for human use. The manufacture of the drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, does not involve the use of any contracted manufacturing facilities as all manufacturing operations are conducted at the Sanofi Pasteur facilities as listed in the table below.

Manufacturing and Testing Responsibilities

Operation	Responsibility	Building
Formulation of the drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, Bulk	Sanofi Pasteur, Inc.	Building (b) (4)
Filling of unit dose vials	Sanofi Pasteur, Inc.	Building (b) (4), Line (b) (4)
Packaging of unit dose vials	Sanofi Pasteur, Inc.	Building (b) (4)
Release and stability testing	Sanofi Pasteur, Inc.	Building (b) (4)
In-vivo stability testing	Sanofi Pasteur (b) (4)	Building (b) (4)

3.2.P.3.2 Batch Formula

Target quantities of the drug substances and buffers used in the formulation of the drug product is presented in the Table below.

Target Composition of Meningococcal Polysaccharide (Serogroups A, C, Y andW135) Tetanus Toxoid Conjugate Concentrate Vaccine Formulation

Ingredient	Reference to Quality Standards	Function	Target Quantity Added ((b) (4) batch)
Meningococcal Polysaccharide, Serogroup A (Monovalent Conjugate)	In house	Active Ingredient	(b) (4)
Meningococcal Polysaccharide, Serogroup C (Monovalent Conjugate)	In house	Active Ingredient	(b) (4)
Meningococcal Polysaccharide, Serogroup Y (Monovalent Conjugate)	In house	Active Ingredient	(b) (4)
Meningococcal Polysaccharide, Serogroup W135 (Monovalent Conjugate)	In-house	Active Ingredient	(b) (4)
Tetanus Toxoid, Filtered Concentrate	In-house	Carrier Protein	(b) (4)
(b) (4) Sodium Chloride Solution	(b) (4)	Excipient used to (b) (4)	(b) (4)
Sodium Acetate, (b) (4)	(b) (4)	Excipient used to (b) (4)	(b) (4)

* Target quantity includes overages of (b) (4) for Serogroup A and (b) (4) for Serogroup C, Y and W135

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

‡ Buffer quantities may vary per batch manufactured.

The buffer composition is (b) (4) Sodium chloride, and (b) (4) Sodium Acetate in (b) (4).

The batch size bulk is approximately (b) (4), and the theoretical yield of the final container is approximately (b) (4) vials.

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

- ❑ The information provided here is adequate. No further information required.

3.2.P.3.3 Description of Manufacturing Process

Formulation of Bulk Vaccine

The Drug Product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, is produced by formulating four Drug Substances comprised of serogroup-specific polysaccharide antigens purified from *Neisseria meningitidis* Serogroups A, C, Y, and W135, separately conjugated to Tetanus Toxoid Protein. The Drug Product vaccine formulation is prepared as a sterile, aqueous solution containing sodium acetate and sodium chloride buffers. Post formulation, the Bulk Drug Product is filled into vials then inspected and stored.

The formulation for the bulk vaccine includes in-process sampling for (b) (4) . In-process testing performed during the manufacture of Meningococcal (Groups A, C, Y, and W135) Polysaccharide Tetanus Toxoid Conjugate Vaccine, Bulk is described in the next section (Section 3.2.P.3.4 Controls of Critical Steps and Intermediates).

Final Container Drug Product

The filling (b) (4) to filling. The (b) (4) The filler is assembled with clean, sterile components.

The bulk vaccine is filled into 2 mL glass serum tubing vials. During the filling operation, the volume accuracy is routinely checked during the run. If any sample is outside the limit of (b) (4) , the fill is stopped immediately and all vials back to the last acceptable (b) (4) check are segregated and discarded. Each vial is stoppered and capped after it is filled, within the filling (b) (4) . The vials are then inspected prior to being labeled, packaged and final released.

Inspection of Unit Dose Vials

Final containers are 100% examined either by manual or fully automated inspection. The site procedures for 100% inspection of parenteral products complies with the requirements set forth in the (b) (4) .
Defects are classified as critical, major or minor. After a 100% inspection, a statistically representative sample is taken for an additional inspection (Major A), the acceptance criteria are:

- Critical Defects: (b) (4)
- Major Defects AQL1: (b) (4)
- Minor Defects AQL: (b) (4)

Information Request Submitted March 18, 2020 (eCTD # 0031)

FDA Question:

Please provide all visual and/or automated inspection results for the finished MenQuadfi DP batches. In addition, please note which lots were inspected manually or automatically.

Sanofi Response:

The inspection results for the (b) (4) MenQuadfi DP batches that were included in the BLA submission along with the inspection results for the last (b) (4) MenQuadfi DP fills that were performed on Line (b) (4) are provided in the Table 13 below. (b) (4) were the 3 validation lots that were inspected in April 2016 using Version 1 of the inspection recipe. (b) (4) was the (b) (4) comparability lot that was filled/inspected in Sept. 2018 using Version 10 of the inspection recipe. (b) (4) were the latest MenQuadfi batches that were filled/inspected on Line (b) (4) and used inspection recipe version 12 and 13 respectively. The higher results that used version 1 of the recipe were expected as a small sample size was used for tuning the initial recipe to reduce the false reject rate. However, the latest batches which used a later version of the recipe and a higher sample size, yielded more typical results (approximately (b) (4) rejection rate). In short, as the recipe was revised/corrected since 2016, the rejection rate has decreased. Please note that inspections are 100% automated.

Table 13: Inspection Results for MenQuadfi DP Fills Performed on Line (b) (4)

Lot Number	Batch End	Version	Infeed Count	Rejection Rate (Total)
(b) (4)				

Reviewer Assessment to IR

Inspections 100% automated for the filled DP. The inspection machine has an (b) (4) that allows visual inspection of rejected containers. It should be noted that this inspection machine has been licensed for Menactra (STN 125089/479) and Fluzone quadrivalent vaccines (STN 103914/5574 and 103914/5672). Although the initial 3 batches shown above in Table 13 had a relatively high false positive rejection rate which was likely due to the inspection programs not being "dialed in". The updated versions (12 and 13) had lower rejection rates (b) (4) which Sanofi claimed was consistent under normal operating conditions. AQL Major A testing also provided evidence of acceptable product presentation (reviewed below). No further inquiries.

Labeling and Packaging of Unit Dose Vials

After inspection, the Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, 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 Pasteur's Quality Department prior to use. The packaged Drug Product is placed in cold storage at 2 ºC to 8 ºC.

Storage of the Drug Product

The expiry for the Bulk Drug Product is (b) (4). The expiry for the Final Container Drug Product is (b) (4) ((b) (4) years) from date of fill at 2°C to 8°C.

Transportation of the Drug Product

The filled Drug Product is transferred from the Capping area to inspection in Building (b) (4) or to a 2°C to 8°C storage area in (b) (4) or designated storage facilities where it remains until it is removed for inspection. Following inspection unlabeled vials are stored in designated warehousing / storage locations. The filled Drug Product is transferred between manufacturing and storage areas via a (b) (4) with a temperature range of 2°C to 8°C. 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.

After inspection and packaging is complete, the final labeled, and packaged product is transferred to the designated warehouse storage facilities via a (b) (4) with a temperature range of 2°C to 8°C. The final labeled and packaged product is stored at 2°C to 8ºC under restricted card access. Finished product is transported to US distribution centers at 2°C to 8ºC using a validated carrier. Temperature monitoring devices accompany every shipment.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- The information provided in this section is acceptable. No further inquiries required.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Control of Critical Steps

The critical process parameters for formulation are the (b) (4). We defer review of the (b) (4) steps to the PO. For the sterile filtration the acceptance criteria for (b) (4), and the (b) (4) test has an acceptance criterion of (b) (4).

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- The validation of the DP bulk and final fill unit dose vials is acceptable. There were no bioburden or sterility excursions demonstrating the manufacturing process is in a state of control. Endotoxin levels were below the acceptance criteria. In addition, no loss in CCIT for tested final vials was noted. The deviations detailed in this section did not result in any invalidation events and were relatively minor. All deviations were investigated, and preventative actions put in place. The data presented here is acceptable and no further inquires required.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

We defer review of this section to the PO.

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

We defer review of these sections to the PO and/or DBSQC.

3.2.P.4.4 Justification of Specifications
We defer review of this section to the PO.

3.2.P.4.5 Excipients of Human or Animal Origin
We defer review of this section to the PO.

3.2.P.4.6 Novel Excipient
We defer review of this section to the PO.

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)

Specification of the Formulated Drug Product (Bulk)

The release tests and acceptance criteria for release of the formulated bulk drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate are provided in the table below.

Release Specification for the Formulated Bulk Drug Product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Test	Compendial Reference	Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)

The release tests germane to this review along with the corresponding acceptance criteria for release of the unlabeled final container drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine are provided in the table below.

Release Specification for the Unlabeled Final Container Drug Product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Test	Compendial Reference	Acceptance Criteria
Bacterial Endotoxin ((b) (4))	(b) (4)	(b) (4)
Sterility	(b) (4)	No Growth
Volume Check	(b) (4)	NLT 0.5 mL/vial
Major A	Non-compendial	Critical Defect: (b) (4) Major Defects AQL (b) (4) Minor Defects AQL (b) (4)

Test	Compendial Reference	Acceptance Criteria
Major B	Non-compendial	Rejects – (b) (4) Rejects – (b) (4)

* AQL: Acceptance quality limit

Specification of the Final Container Drug Product (Labeled)

See table below. The review of this section is deferred to the PO.

Release Specification for the Labeled Final Container Drug Product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Test	Compendial Reference	Acceptance Criteria
Identity of Carrier Protein and Polysaccharide Group	Non-compendial	Carrier protein – (b) (4) Carrier protein – (b) (4) Polysaccharide group- Identifies as group A, C, Y, and W135 polysaccharide

Justification of Specification of Formulated Drug Product Bulk

(b) (4)

Justification of Specification of Unlabeled Final Container Drug Product

Here I will only review the sterility, endotoxin, and Major A justifications. The remainder I will defer to the PO for review.

Bacterial Endotoxin ((b) (4))

Determination of bacterial endotoxin content is a required safety test for release. Meningococcus is a gram-negative bacterium with inherent endotoxin activity. This assay is compliant with compendial methods from the (b) (4).

Specification: (b) (4)
Justification: The endotoxin limit specification is based on the threshold pyrogenic dose for a 2-year-old child. The (b) (4) requirement is (b) (4) (dose: 0.5 mL).

(b) (4)
See above justification for formulated bulk DP.

Physical Appearance (Major A)
Preparation of injectable products requires that each final container vaccine be subjected to a physical inspection, referred to as the 100% inspection process. The acceptance quality limit (AQL) inspection of final containers is performed as an audit of the 100% inspection process.

Specification: Major Defects: AQL (b) (4), Minor Defects: AQL (b) (4), Critical Defects: (b) (4)
Justification: The AQL inspection is the visual examination of the container, closure, and product for defects. Critical ((b) (4)): A defect that would adversely affect the safety, efficacy, purity, or quality of the product; one that would prevent the essential unit performance or; one that would likely result in market withdrawal. Major (AQL (b) (4)): A defect, other than critical, that would not likely reduce the safety, purity, or efficacy of the product; would likely reduce the usability of the product; or which may be viewed by the user as unacceptable. Minor (AQL (b) (4)): A defect that may affect the appearance of the unit but will not affect its form, fit, or function. Based on batch size, the sum of defect units for each defect category is compared to the category AQL limit and corresponding accept/reject values to determine if the 100% inspection process was acceptable or not.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:
- The specifications and justifications provided by the Firm and reviewed in this memo are adequate to ensure a safe product. No further inquiries required.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures
The list of analytical procedures for release testing of drug product pertaining to the purview of this review are presented here.

The test for Bulk Drug product is (b) (4) reference number Q_0277776.

The tests for unlabeled final container Drug Product and reference number are listed below.

- Bacterial Endotoxin ((b) (4)) Reference number Q_0233845
- Sterility Reference number Q_0277776
- Physical Appearance Major A Reference number Q_0281004

For this memo I will only review the sterility, endotoxin, and major A procedures. The remainder I will defer to the PO for review.

Sterility

The (b) (4) method of sterility testing is performed on the (b) (4) unlabeled final container drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine. The sterility test is used to determine the presence of extraneous viable contaminating micro-organisms in test samples. The sterility test conforms to (b) (4) test requirements for no microbial growth in the drug product.

The sterility test is a compendial method and as such must be verified by demonstrating method suitability/specificity in the presence of product. The drug product was assessed for non-interference in the sterility test by demonstration of the ability to support the growth of low levels of microorganisms. (b) (4)

All results passed the acceptance criteria listed above demonstrating there was no bacteriostatic or fungistatic activity of the drug product.

Bacterial Endotoxin

The bacterial endotoxin test by the (b) (4) method is performed on the unlabeled final container drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine. This test is performed in compliance with the (b) (4).

(b) (4)

Compendial methods must be verified for use; therefore, the characteristics assessed were (b) (4). Method verification was performed using (b) (4) lots of the drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine. Drug product samples were prepared at a (b) (4) as determined by the (b) (4). The coefficient of variation (CV) must be (b) (4)

(b) (4)

Major A Testing

The Major A test is performed on the unlabeled final container drug product, Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine, to ensure that the vaccine complies with Major A inspection standards for an acceptable product appearance. During the 100% visual product inspection, the actual product appearance is compared with the product description. The 100% inspection of parenteral products complies with the requirements set forth in the (b) (4) . An acceptance quality limit (AQL) inspection for Major A is performed as an audit of the 100% visual inspection and also complies with (b) (4) . The visual inspection workstation utilized for inspection is in compliance with (b) (4) .

Each final container selected for Major A testing is examined (b) (4) 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) .

All testing is evaluated for critical defects at (b) (4) AQL, major defects at (b) (4) AQL and minor defects at (b) (4) AQL. (b) (4) the batch is considered unacceptable and does not meet requirements.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

- The analytical procedures for sterility, endotoxin, and Major A testing are standard procedures for release testing. The information provided here is adequate, not further inquiries.

3.2.P.5.4 Batch Analyses

Batch analysis for the PPQ batches was presented above in Section 3.2.P.3.5-Process Validation and/or Evaluation and will not be repeated here.

3.2.P.5.5 Characterization of Impurities

Endotoxin results were presented above in Section 3.2.P.3.5 Process-Validation and/or Evaluation and will not be repeated here.

3.2.P.6 Reference Standards or Materials

There are none for the drug product.

3.2.P.7 Container Closure System

(b) (4)

Primary Packaging

The Meningococcal (Serogroups A, C, Y, and W135) Polysaccharide Tetanus Toxoid Conjugate Vaccine, Unit Dose Vials are filled in 2 mL, United States Pharmacopoeia (USP) Type I borosilicate clear glass with a 13 mm butyl (Latex Free) stopper and a flip off seal. The vial material from vendor meets (b) (4) . The stopper material from vendor meets (b) (4) The vial dimensions are listed as follows:

- Overall length: 31.5 to 32.5 mm (1.240 to 1.280 inches)
- Body Outside Diameter: 14.5 to 15.0 mm (0.571 to 0.591 inches)
- Finish Inside Diameter (Neck): 6.86 to 7.24 mm (0.270 to 0.285 inches)
- Finish Outside Diameter (Lip): 12.95-13.34mm (0.510 to 0.525 inches)
- Lip Thickness: 3.73-4.11mm (0.147 to 0.162 inches)

The dimensions of the Butyl Stoppers are listed as follows:

- Stopper Diameter: 12.45 to 12.95 mm (0.490 to 0.510 inches)
- Flange Thickness: 1.803 to 2.184 (0.071 to 0.086 inches)
- Plug Diameter: 7.49 to 7.75 mm (0.295 to 0.305 inches)

When the vials are received on site, they are (b) (4) . The tests performed on each batch are as follows:

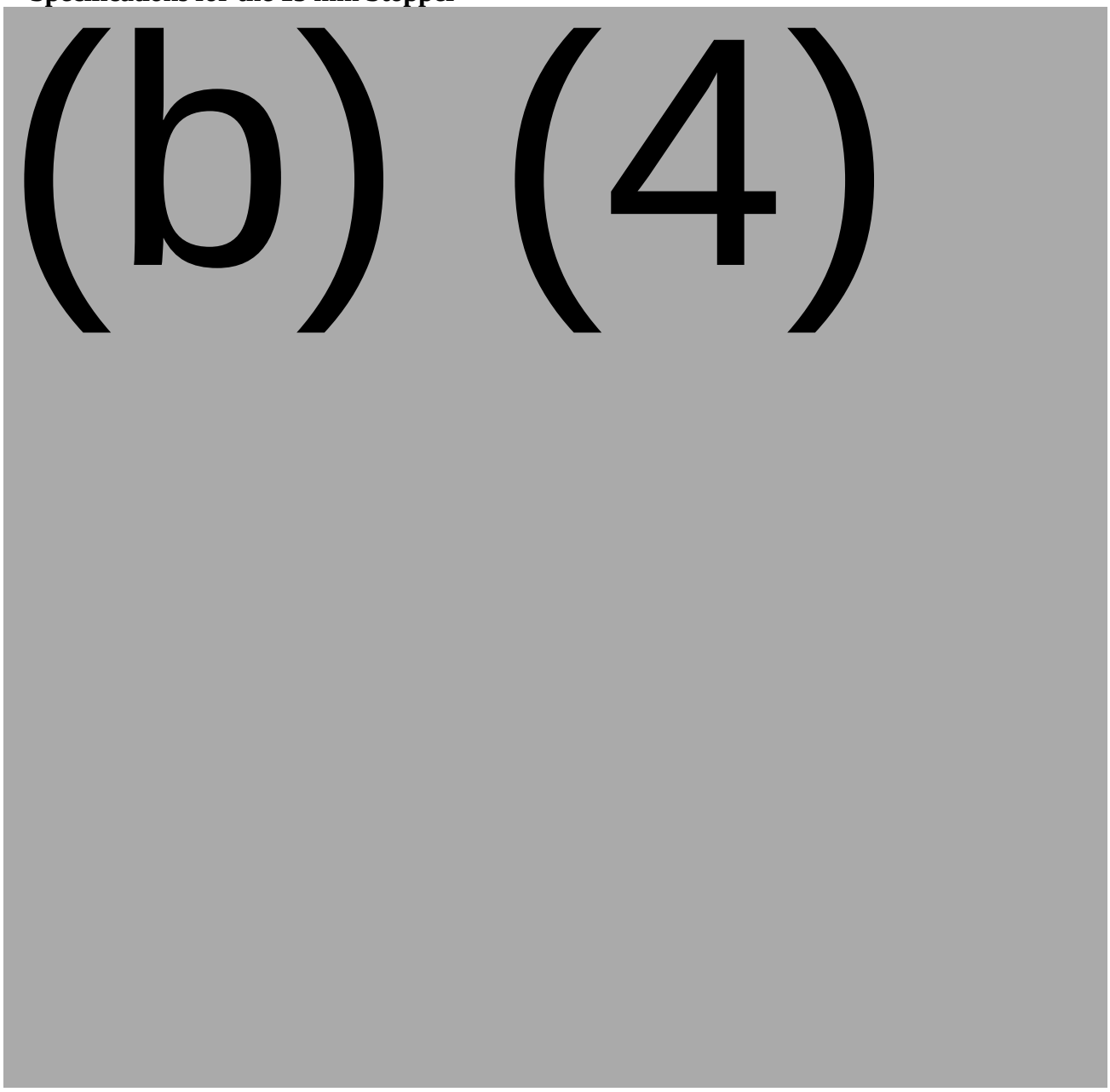
- Visual Inspection ((b) (4) , etc).
- Verification of dimensions.

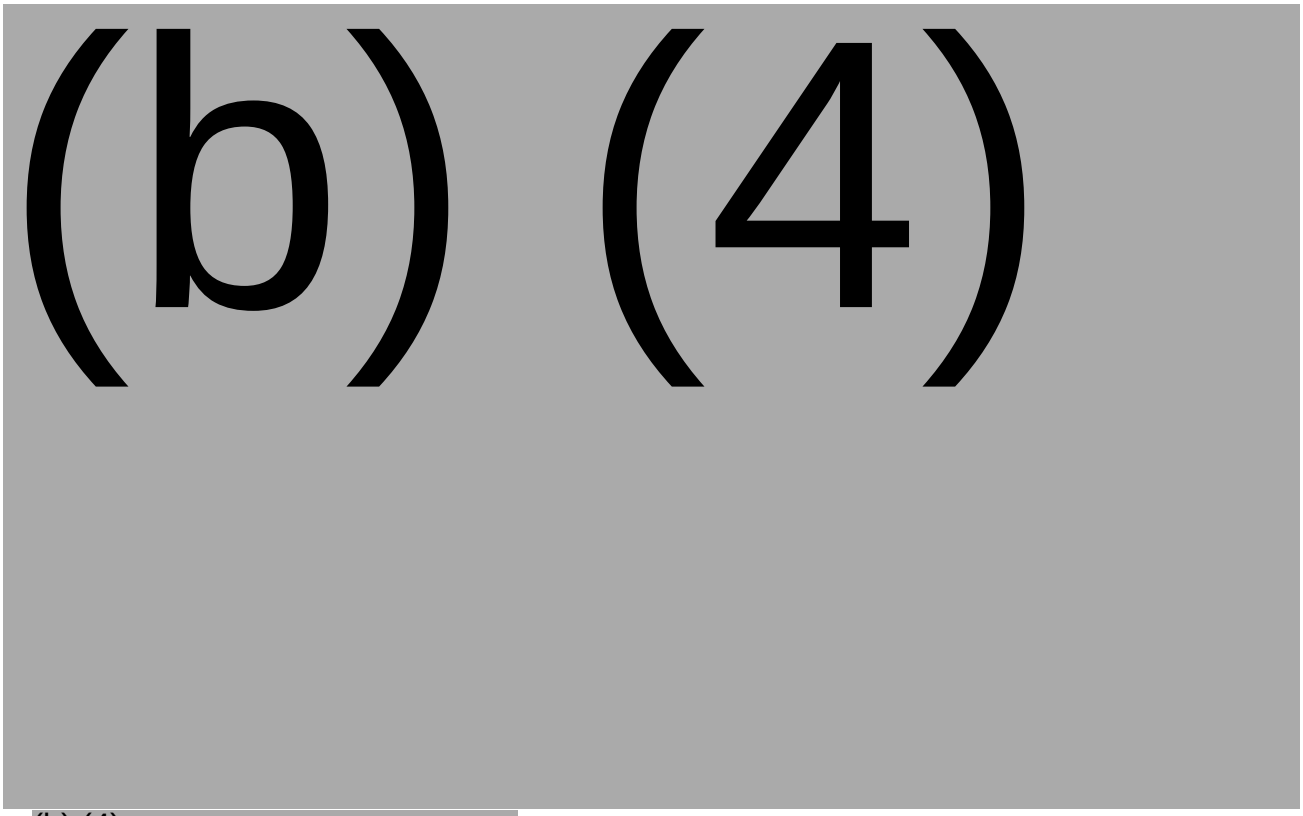
- Document check, Certificate of Compliance from supplier.

The specification for the 13 mm stopper is provided in the table below. Stoppers are received (b) (4) from the supplier and (b) (4) sterilized on site prior to use. The tests performed on each batch are as follows:

- Visual Inspection ((b) (4) , etc.).
- Verification of dimensions.
- Document check, Certificate of Compliance from supplier.

Specifications for the 13 mm Stopper





(b) (4)
†NMT: not more than
(b) (4)
(b) (4)

Suppliers for the 2 ml vial and 13 mm stopper are provided in the table below.

Suppliers

Item	SUPPLIER AND ADDRESS
2 ml Vial	(b) (4)
13 mm Stopper	(b) (4)

Secondary Packaging
The filled vial with stopper is crimped-sealed with flip off seal, made of aluminum skirt that is fitted with a 13 mm plastic cap. This packaging material is not in contact with the product. The dimensions for the flip off seal are listed below.

- Seal Skirt Length: 6.17 to 6.38 mm (0.243 to 0.251 inches)
- Seal Inside Diameter: 13.36 mm (0.526 inches) minimum

The tests performed on each batch are as follows:

- Visual Inspection ((b) (4) …).
- Verification of dimensions.
- Document check from supplier.

Overall Reviewer's Assessment of Section 3.2.P.7:

- The information provided in this section provides adequate information regarding the primary container closure system. No further information required.

3.2.P.8 Stability

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

(b) (4)

(b) (4)

Tetanus Toxoid Conjugate Vaccine Unit Dose Vials

Stability studies have been initiated for the final DP in unit dose vials (2 mL Type I borosilicate clear glass vials with 13 mm butyl stoppers) stored at 2-8°C for (b) (4) . Accelerated stability studies were also conducted for DP unit dose vials stored at (b) (4) . (b) (4) commercial scale lots ((b) (4)) were placed on stability for (b) (4) to support a (b) (4) expiry point. Currently 36 months of data have been provided for drug product stored at 2-8°C, and the accelerated stability studies stored at (b) (4) have been completed.

The following analytical tests were conducted to support the stability studies.

- Total Polysaccharide
- Free Polysaccharide
- (b) (4)
- Physical Examination
- Sterility
- (b) (4)
- Container Closure Integrity

For the purpose of this review I will focus only on the sterility and CCIT data, the remainder of the results we defer to the PO for review.

For lots (b) (4) , 36 months of data is currently available for review. All (b) (4) lots passed sterility testing up to the 36-month timepoint and all have passed the container closure integrity testing.

The newer supplementary lot (b) (4) was place on stability in July of 2018. Presently the 12-month stability data is pending but currently there have been no testing failures with this lot.

The accelerated stability studies which were held at (b) (4) have been completed for all (b) (4) lots ((b) (4)). Sterility and container closure were tested at the (b) (4) timepoints. All (b) (4) lots passed acceptance criteria and no failures were noted.

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

Sanofi commits to completing the on-going studies performed on the Drug Product, Meningococcal (A, C, Y W135) Polysaccharide Tetanus Toxoid Conjugate Vaccine Bulk stored under normal storage conditions ((b) (4)) and Unit Dose Vial stored under normal storage conditions (2°C to 8°C) according to approved stability protocols.

In addition, Sanofi commits to placing at least (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 test methods and acceptance criteria for the stability study are identical to those applied at release of the bulk and unit dose vial with the exception of the container closure integrity test (CCIT) and physical examination.

Overall Reviewer's Assessment of Section 3.2.P.8:

- Sanofi wants an expiry of (b) (4) for the finished DP in unit vials. At this point only 36 months of data has been provided for the (b) (4) lots of DS manufactured in (b) (4), and only 9 months of data for the one lot manufactured in (b) (4). At present there have been no issues with the DP held at 36 months in terms of sterility and CCIT. However, I would be against a (b) (4) expiry until at least one of the stability lots has been tested at (b) (4) which will occur in April of 2020; however, final determination regarding this is the responsibility of OVRR. In terms of the accelerated hold time conditions those studies were completed and there were no failures in terms of sterility of CCIT. The data appears to be adequate and no further inquiries are required.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Below is a table which lists the manufacturing facilities listed in the submission along processes performed at each.

Facility Table for BLA 125701/0

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
Process(es): Drug substance manufacturing, final bulk product formulation, filling and packaging of unit dose vials, quality control, release and stability testing. **Facility**: Sanofi Pasteur, Inc.	Waiver	Yes	yes	**Most recent inspection:** June 6-15, 2018 Surveillance and Post-approval Inspection (STN 125559) TeamBio Inspection classified as VAI.

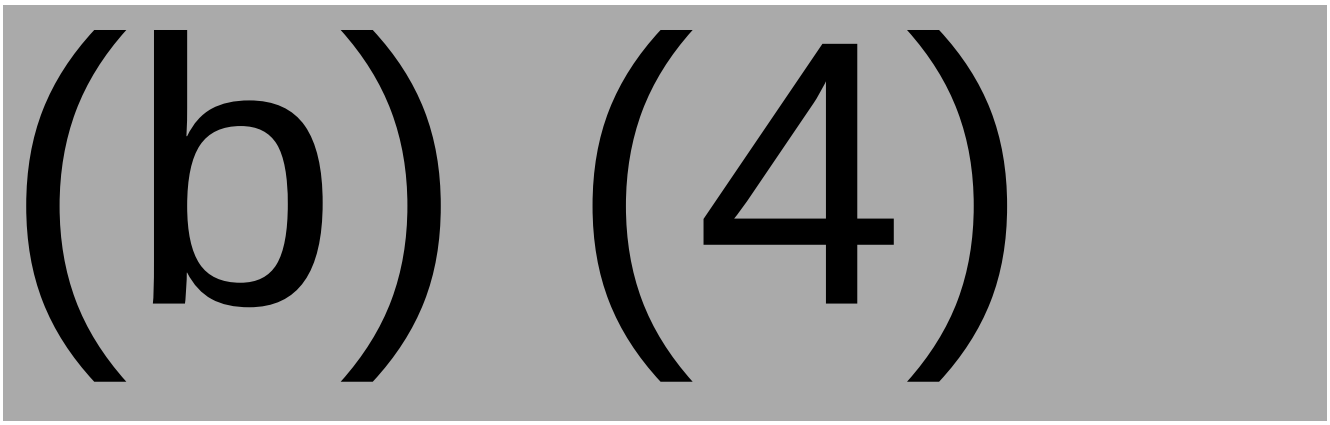
1 Discovery Drive Swiftwater, PA 18370 **FEI**#: 2518760				
Process(es): Bulk Drug Substance manufacture (Tetanus Toxoid), quality control, release and stability testing. **Facility**: Sanofi Pasteur (b) (4) **FEI**#: (b) (4)	Waiver	Yes	yes	**Most recent inspection:** (b) (4) Surveillance Inspection TeamBio. Inspection classified as VAI.
Process(es): In vivo stability testing **Facility**: Sanofi Pasteur (b) (4) **FEI**#: (b) (4)	No	Yes	Yes	**Most recent inspections:** (b) (4) Surveillance Inspection Conducted by TeamBio. Inspection classified as VAI. A surveillance inspection was recently conducted by TeamBio from (b) (4). No 483 was presented.

Drug Substance Manufacturing

The tetanus toxoid is manufactured at the Sanofi Pasteur (b) (4) site, in Buildings (b) (4). This is an FDA approved facility for the manufacture of tetanus toxoid and there are no process changes for the manufacture of tetanus toxoid in this submission ((b) (4)). In addition, this facility has an acceptable compliance history, and therefore will not be reviewed here.

Likewise, the meningococcal polysaccharide purification, conjugation process of polysaccharide to TT, and the formulation and final fill of the Men-TT drug product are conducted the in FDA-licensed buildings (b) (4). Building (b) (4) is dedicated for the manufacture of meningococcal polysaccharide vaccines and was licensed for the manufacture of purified meningococcal polysaccharides (A and W135 STN 125089/407; and C and Y STN 125089/437), and *N. meningitidis* Polysaccharide Diphtheria Toxoid Conjugate Concentrates, Serogroups A, C, Y, and W135 (for use in Menactra, STN 125089/536 and 125089/543). The manufacturing of the

Drug Substances, *N. meningitidis* Polysaccharide Tetanus Toxoid Conjugate Concentrates (for use in MenQuadfi) did not require any facility or utility changes to switch from the manufacturing of *N. meningitidis* Polysaccharide Diphtheria Toxoid Conjugate Concentrates (for use in Menactra), the currently licensed product in (b) (4).



Drug Product Manufacturing (Building (b) (4))

The formulation and filling of Drug Product MenQuadfi Vaccine will occur in Building (b) (4) and utilizes (b) (4) during formulation and 2mL glass serum vials and 13mm latex free stoppers during filling. Formulation of the vaccine will occur on Skid (b) (4) and vial filling will occur on Line (b) (4). Both formulation and filling processes have been validated.

Building (b) (4) was initially licensed in 2008. A PAI of the facility occurred from 06 through 10 October 2008 under STN 1039164/5212 for Fluzone and the resulting inspectional observations have been completed and closed. Thereafter, additional products have also been licensed to be formulated and filled in (b) (4) and are detailed below.

For the formulation process the following equipment and the corresponding licensed product(s) are presented below.

For the filling process the following equipment, (b) (4) , Capping, have all been licensed for the following products listed below:

The (b) (4) used for (b) (4) of Line (b) (4) change parts and 13 mm stoppers has been licensed for the following products:

9

The inspection machine, (b) (4) has been licensed for the following products:

Building (b) (4) is currently a multi-product formulation and filling facility. The manufacturing of the Drug Product, MenQuadfi Vaccine in (b) (4) did not require any facility or utility changes to support validation activities and did not introduce any new drug product equipment not already included in a licensed product already approved by CBER as described in the table above. As this is an already approved manufacturing facility and no additional building changes were required no further review of this building is necessary.

New Equipment in (b) (4)

The equipment used in the manufacture of the *N. meningitidis* polysaccharide purified bulk (b) (4) (Serogroups A, C, Y, W135) is the same for both MenQuadfi (b) (4) which was previously approved ((b) (4)).

There are (b) (4) new pieces of product-contact equipment used in the production of the *N. meningitidis* polysaccharide tetanus toxoid conjugates which are the following:

(b) (4)

IQ/OQ testing was executed to verify the equipment functioned properly for its intended purposes. Performance qualification of the equipment was demonstrated during the execution of the PV lots as presented above. There were no deviations associated with the new equipment.

(b) (4)

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

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.A.1:

- For this submission there are very few changes being implemented. All the buildings are currently approved for the required manufacturing steps and all have an acceptable compliance history. The major pieces of equipment that are new for MenQuadfi were reviewed here, and from the data provided they appear to be working adequately. There were no major issues with the cleaning validations. The deviations that occurred were minor and resolved. The information provided here is acceptable since there are very few changes being implemented. No further inquiries required.

3.2.A.2 Adventitious Agents Safety Evaluation

We defer review of this section to the PO.

3.2.A.3 Novel Excipients

None

3.2.R Regional Information (USA)

- **Executed Batch Records**

Executed batch records were not included with the original submission but were provided in amendment STN 125701/0.4 (eCTD # 0005) upon request by the PO.

- **Method Validation Package**

These were provided and discussed in the above sections 3.2.S.4.2 and 3.2.S.4.3 and 3.2.P.5.2 and 3.2.P.5.3.

- **Combination Products**

N/A

- **Comparability Protocols**

Two comparability protocols were submitted. Both are regarding tetanus and meningococcal seed banks. We defer to the PO for review of this section.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Sanofi requests a categorical exclusion from the requirement to prepare an EA under 21 CFR § 25.31(c). To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.