



To: BLA STN 125682/0, Dengue Tetravalent Vaccine (Live, Attenuated) (Dengvaxia)
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Subject: Review of the BLA submitted by **Sanofi Pasteur Inc., Lic. # 1725**, for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in persons 9 through 17 years of age living in endemic areas.
Due Date: May 1, 2019

REVIEW RECOMMENDATIONS

Approval of the following:

1. Drug Substance manufacture at Sanofi Pasteur facility at (b) (4)
FEI#(b) (4)
2. Drug Product manufacture at Sanofi Pasteur SA facility at (b) (4)
FEI#(b) (4)
3. Diluent manufacture at Sanofi Pasteur Inc. facility at Swiftwater PA, USA
FEI#2518760
4. Quality Testing facility at Sanofi Pasteur Ltd. facility at Toronto, Canada
FEI#3002888623

REVIEW SUMMARY

Sanofi Pasteur Inc. (SP) submitted a BLA under STN 125682/0 for the licensure of Dengue Tetravalent Vaccine (Live, Attenuated) (Dengvaxia). The Pharmacological Class for the vaccine is the Anatomical Therapeutic Chemical Classification System (ATC) code of the CYD dengue vaccine is J07BX, i.e. J (ANTIINFECTIVES FOR SYSTEMIC USE) 07 (VACCINES) B (VIRAL VACCINES) X (Other viral vaccines). The BLA initially proposed indication is for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in persons 9 through 45 years of age living in endemic areas. After discussion with CBER based on available clinical data, on April 1, 2019, Sanofi has decided to seek licensure for children and adolescents aged 9 - <17 years of age. They will not seek licensure for individuals 17 – 45 years of age at this time. The package contains a vial of lyophilized vaccine component and a 0.6 mL vial of saline diluent (0.4% Sodium Chloride). The reconstituted drug product solution is for subcutaneous use only. The primary vaccination schedule consists of three injections of one reconstituted dose (0.5 mL) to

be administered at six-month intervals (month 0, 6, and 12). When Dengvaxia is reconstituted with saline diluent (0.4% sodium chloride), each 0.5 mL dose is formulated to contain 4.5 - 6.0 log₁₀ CCID₅₀ of each chimeric yellow fever dengue (CYD) virus serotypes 1, 2, 3, and 4 per dose. The BLA was submitted by SP and received by CBER on August 31, 2018.

CBER performed Pre-License Inspection (PLI) at SP's facilities in (b) (4) from (b) (4) to support the review of STN 125682/0. The (b) (4) facilities are used for the manufacture of the drug substance (DS) and drug product (DP) respectively. The inspectional findings for both facilities are documented in the Establishment Inspection Reports (EIR) and available in the eNSpect application.

Information Requests (IR) from DMPQ were communicated to the firm on 9/28/2018, 10/12/2018, 10/26/2018, 11/1/2018, 11/20/2018 and 4/9/2019. The firm provided responses to these IRs in Amendments STN125682/0.3, STN125682/0.7, STN125682/0.11, STN125682/0.13 and STN125682/0.45 respectively. Reviews of these amendments are incorporated in this memo and no separate addendum is prepared.

NARRATIVE REVIEW

The review is organized in the following sections:

- I. ITEMS REVIEWED**
- II. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL**
- III. DENGVAXIA MANUFACTURING PROCESS OVERVIEW**
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 - 2. PRODUCT DESCRIPTION**
- IV. DRUG SUBSTANCE**
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 - 2. DS MANUFACTURING PROCESS**
 - 3. EQUIPMENT for DS MANUFACTURING**
 - 4. VALIDATION FOR BDS MANUFACTURING PROCESS**
 - 5. PROCESS PERFORMANCE QUALIFICATION STUDIES (PPQ)**
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- VI. DRUG PRODUCT (DILUENT 0.4% NaCl)**
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 - 3. DILUENT MANUFACTURING PROCESS VALIDATION**
- VII. REVIEW ISSUES AND CONCLUSION**

- I. ITEMS REVIEWED**
 - STN 125645/0

- STN 125682/0.3 9/28/2018 For CE request
- STN 125682/0.7 10/12/2018 For QC tests at all production facilities
- STN 125682/0.9 10/26/2018 FEI # issues for (b) (4), production schedules
- STN 125682/0.11 11/1/2018 CMC related issues
- STN125682/0.13 11/30/2018 Critical Equipment PQ and EM data
- STN125682/0.45 4/12/2019 Diluent CCIT

I reviewed the manufacturing processes of Dengvaxia to include the DS (b) (4)) performed at Sanofi's facility in (b) (4) and DP (formulation, filling, and lyophilization) performed at Sanofi's facility (b) (4), as well as the manufacturing of the diluent performed at the Sanofi's Swiftwater facility in PA.

My review focused on the facilities, equipment, sterilization, lyophilization, container closure integrity testing, and the filling and packaging.

II. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

Categorical Exclusion

Sanofi requested a categorical exclusion (CE) from the requirement to prepare an environmental assessment under 21 CFR § 25.31(a) in the BLA Section **1.12.14**. SP stated that to their knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment. SP indicated that the Dengvaxia vaccine is derived from a naturally occurring source material whose environmental presences will not be increased through manufacture of the product and it is indicated for treatment of a rare disease, the exemption according to 21 CFR 25.31 (c) "Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, 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." is appropriate.

Reviewer's comment:

SP was informed that the CE should be requested under 25.31(c) as agreed upon with the Agency during the type B meeting dated September 29, 2106.SP submitted amendment STN 125682/0.3 on Sept. 28, 2018 to request the CE under 25.31(c). Based on the information submitted and the nature of this product, I concluded that the sponsor's request for Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) is justified as this product is composed of naturally occurring substances and manufacturing of this product will not alter significantly the concentration and distribution of the natural substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

III. DENGVAIXA MANUFACTURING PROCESS OVERVIEW

1. FACILITIES (DS, DP and Testing)

The following facilities in Table 1 are associated with the manufacture and testing of drug substance

(DS), drug product (DP), and diluent.

Table 1. Dengvaxia, Dengue Tetravalent Vaccine (Live, Attenuated) Facilities

Manufacturing/ Testing Activities	Facility	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Inspections
<ul style="list-style-type: none"> • Manufacture of the Drug Substance • Quality Control testing of Drug Substance • Quality Control testing of Drug Product including release testing 	Sanofi Pasteur (b) (4) [REDACTED] FEI (b) (4) DUNS (b) (4)	Inspection	Yes	Yes	No prior FDA inspection history
<ul style="list-style-type: none"> • Manufacture of the Drug Product • Quality Control testing of Drug Product including release testing 	Sanofi Pasteur SA (b) (4) [REDACTED] FEI (b) (4) DUNS (b) (4)	Inspection	Yes	Yes	No prior FDA inspection history
<ul style="list-style-type: none"> • Quality Control Testing (Vaccine) 	Sanofi Pasteur SA (b) (4) [REDACTED] FEI (b) (4) DUNS (b) (4)	Not Required	No	Yes	(b) (4) VAI (b) (4) VAI
<ul style="list-style-type: none"> • Final Bulk Product Formulation (Diluent) • Filling (Diluent) and Packaging (Vaccine and Diluent) • Quality Control (Vaccine and Diluent) and Stability Testing (Diluent) 	Sanofi Pasteur, Inc. (SWR) Discovery Drive Swiftwater, PA 18370-0187 FEI 2518760 DUNS 086723285	Waiver	Yes	Yes	10/22-26/2018 6/6-15/2018 06/14-22/2016 All VAI
<i>In vivo</i> Quality Control testing of Diluent for release	Sanofi Pasteur Ltd. 1755 Steeles Avenue West Toronto, Ontario M2R 3T4 Canada FEI 3002888623 DUNS 208206623	Waiver	Yes	Yes	9/6-22/2017 VAI

Table 2: Operations and Responsibilities of Sanofi Pasteur

Operation	Location			
	(b) (4)	(b) (4)	(b) (4)	Swiftwater (SWR)
Manufacture of the Drug Substance			X	
Manufacture of the Drug Product	X			
Secondary packaging/labelling of final Product				X
Quality control	X	X	X	X
Final packaged product batch release				X

Reviewer's comment:

Inspections are carried out for the DP manufacturing facility at the Sanofi Pasteur (b) (4) site from (b) (4) and DS manufacturing facility at (b) (4) site from (b) (4) respectively. FDA Form 483 were issued upon conclusions for both facilities. See EIRs for both sites for details. Inspections for the Sanofi Swiftwater PA and Sanofi Toronto, Canada facilities were waived. See inspection waiver memo for details.

2. PRODUCT DESCRIPTION

The CYD dengue vaccine, Dengvaxia, is a live attenuated dengue tetravalent vaccine containing four recombinant viruses expressing the surface antigens of each dengue serotype on a yellow fever viral backbone. Each monovalent CYD dengue virus was obtained separately via recombinant deoxyribonucleic acid (DNA) technology. The CYD dengue viruses were constructed by replacing the gene encoding the pre-membrane (prM) and envelope (E) proteins of the structural proteins in the attenuated yellow fever (YF) 17D virus genome by the corresponding genes of the 4 wild type dengue virus serotypes 1, 2, 3 and 4. The immunizing antigens are the prM and E proteins from dengue virus serotypes 1 to 4.

Dengvaxia is a sterile and freeze-dried product to be reconstituted before injection with a sterile solution of 0.4% sodium chloride for the single dose presentation. The vaccine is presented in a single-dose vial, and the diluent (0.4% NaCl) also provided in a vial is co-packaged in the final product package. The vaccine contains neither an adjuvant nor a preservative, and after reconstitution, each 0.5 mL dose contains ~5 log₁₀ cell-culture infectious dose 50% (CCID₅₀) per dose of each live, attenuated, dengue virus serotype 1, 2, 3 and 4.

The proposed indication for the CYD dengue vaccine is active immunization for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Once the freeze-dried vaccine has been completely reconstituted with the supplied diluent, it is administered via the subcutaneous (SC) route.

The Anatomical Therapeutic Chemical Classification System (ATC) code of the CYD dengue vaccine is J07BX, i.e. J (ANTIINFECTIVES FOR SYSTEMIC USE) 07 (VACCINES) B (VIRAL VACCINES) X (Other viral vaccines).

The Drug Substance (DS) is produced on serum-free Vero cell culture by (b) (4)

(b) (4). The virus is harvested and (b) (4) before being subjected to purification by (b) (4) chromatography. The harvest is then concentrated / (b) (4) to reach the expected virus concentration before being stabilized, (b) (4) which constitute the bulk DS.

The manufacturing process of the CYD dengue vaccine DP consists of formulation and fill/freezing-drying steps. During the formulation step, the four bulk DS are (b) (4) mixed together with stabilizing solution to obtain the specified composition of each virus serotype. The formulated Final Bulk Product (FBP) is then sterile filtered with 0.2 µm filter, filled into 3 mL glass vials and then lyophilized to obtain the CYD dengue vaccine DP.

IV. DRUG SUBSTANCE (CYD DENG VAXIA)

1. FACILITIES for DS MANUFACTURING

The manufacturers for CYD dengue DS is at the SP's (b) (4) facility. All facilities involved in CYD DS manufacturing are summarized in Table 3.

Table 3: Manufacturer of the CYD Dengue Drug Substance

Manufacturer name	Manufacturer address	Manufacturing operation
Sanofi Pasteur	(b) (4)	Quality control of the Drug Substance
Sanofi Pasteur (b) (4)	(b) (4)	Manufacturing of the Drug Substance
		Quality control of the Drug Substance

The manufacturing of the CYD dengue monovalent bulk is (b) (4). (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)


3.1. Equipment Cleaning

There are (b) (4) different cleaning systems used in building (b) (4) to clean equipment in direct contact with the product:

(b) (4)


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(b) (4)

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(b) (4)

(b) (4)

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(b) (4)

(b) (4) Process Validation

(b) (4) validation for equipment has been conducted using worst case conditions based on risk assessment.

Regarding the cleaning process validation, the following conditions are applied:

(b) (4)

(b) (4)

(b) (4)

B. Industrial Part Washer

There is one industrial part washer in building (b) (4), and the equipment washed by this washer are listed in the Table below:

(b) (4)

The industrial part washer is (b) (4) equipped, installed between the washing area (room (b) (4)) (“dirty side”) and the material preparation area (room (b) (4)) (“clean side”). IQ/OQ studies have been carried out. The washer uses only (b) (4) for the washing process followed with (b) (4) cycle. Cleaning validations were conducted using worst case conditions using representative equipment for the study. (b) (4) were used as physical-chemical indicator along with (b) (4) as microbiological indicators in the acceptance criteria. The test condition and acceptance criteria are summarized in the table below:

(b) (4)

(b) (4)

Reviewer's comment

The cleaning validation studies for (b) (4) and processing tanks were conducted and the results met acceptance criteria. DHT and CHT for these equipment have also been validated.

C. Washing Machine

There are (b) (4) wash machines in Building (b) (4) used for small equipment for Dengvaxia production. The washing machines are (b) (4) equipped, installed between the washing area (b) (4) and the material preparation area (b) (4). The following equipment are washed by the washing machines:

Table 17: Equipment cleaned by wash machine

(b) (4)

Cleaning solutions used are prepared with (b) (4)

Validation runs have been conducted for all (b) (4) wash cycle processes with at least (b) (4) acceptable (b) (4).

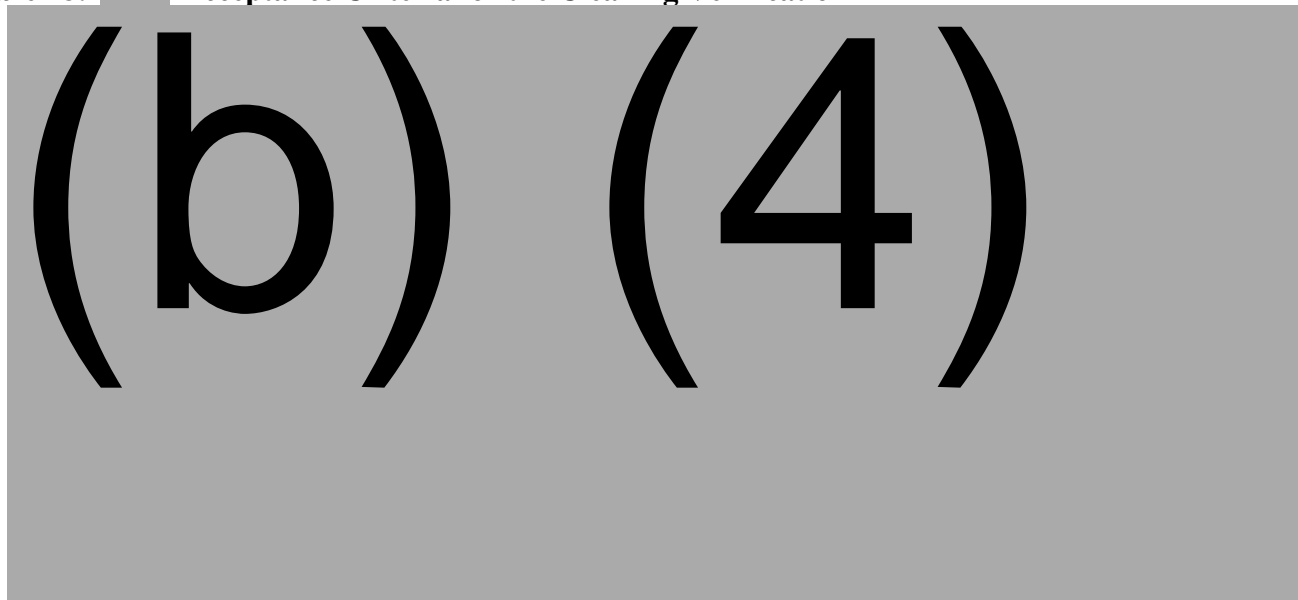
(b) (4)

IQ/OQ studies for the (b) (4) system were completed.

Reviewer's comment:

Based on the cleaning validation results reviewed, the cleaning systems used in building (b) (4) to clean equipment in direct contact with the product, were validated for each cleaning Systems, including the (b) (4), Industrial part washer and the washing machines. The acceptance criteria for both the physical-chemical and micro bacterial indicators appear adequate. It is noted that some of the (b) (4) rinse acceptance for (b) (4) samples were (b) (4) which appeared higher than the (b) (4) standard as shown in the table below:

Table 18: (b) (4) Acceptance Criteria for the Cleaning Verification



Firm used (b) (4) to calculate these acceptance criteria based on toxicity calculations. These are upstream processing equipment, and based on the data, the validation results are acceptable. During PLI, the inspection team brought up the issue that the (b) (4) limit for (b) (4) is high considering as final (b) (4) rinse samples with Sanofi management, and Sanofi acknowledged that the (b) (4) for rinse samples is high, and they will adjust the limit lower, since the actual data available were in much lower range. See EIR for more review of this issue. Maximum DHT for all equipment have been defined with these studies. Verification of the validated status of the cleaning system is required. Based on the cleaning validation results and on the processes capability, alert limits are being determined as well during the verification studies. All deviations in the studies were addressed. During the inspection of the (b) (4) facility, equipment cleaning validations have been extensively reviewed, see EIR for (b) (4) facility for more details.

3.2. Equipment Decontamination and Sterilization

A. Decontamination:

Decontamination is done for the following equipment:

(b) (4)



(b) (4)

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(b) (4) methodologies are available in building (b) (4) as summarized in the table below:


(b) (4)

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Table 19: Decontamination Systems Used in Building (b) (4)

(b) (4)

(b) (4)

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(b) (4)



3.3. Qualification of Critical Equipment

(b) (4)



The firm claimed the installation Qualification (IQ) and Operational Qualification (OQ) studies were completed. Cleaning Decontamination and sterilization were also validated as reviewed in “Equipment cleaning, Decontamination and Sterilization” sections of this memo.

(b) (4)



(b) (4)



G. Computer System

The computer systems in Building (b) (4) consists of two systems:

- A process control system (PCS) is deployed in order to allow the monitoring, the data recording and the control of process equipment and utilities systems. It ensures proper process sequencing and automatically captures comprehensive records for regulatory compliance.
- A Manufacturing Execution System (MES) is installed as a complementary tool to the PCS in order to optimize equipment control and manufacturing operation follow-up. MES

There is minimal information for the systems provided in the BLA submission, other than stating that IQ/OQ/PQ for the computer systems were conducted. The validations of these systems were reviewed during the PLI. See EIR for details.

4. VALIDATION FOR BDS MANUFACTURING PROCESS

The process validation is based on the demonstration of the process consistency i.e., its ability to manufacture a product of the required and reproducible quality by running the Critical Process Parameters (CPPs) at their target values and within their operating ranges or limits. CPPs are monitored during the

validation studies for each of the manufacturing process stage. The product attributes are also followed to assess the product quality and product consistency during the validation by manufacturing stage. These product attributes include:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

5. PROCESS PERFORMANCE QUALIFICATION STUDIES (PPQ)

(b) (4) consecutive batches for each serotype, *i.e.* (b) (4) batches of the CYD dengue Drug Substances were manufactured at (b) (4) industrial scale resulting in a batch size around (b) (4). The batch

(b) (4)

G. Environmental Monitoring Data during PPQ Campaign

Sanofi provided EM data covering the time when (b) (4) PPQ DS batches were manufactured at the (b) (4) facility from October 2013 to May 2014 in Amendment 13. The EM data is from the (b) (4) area and (b) (4) area, and the results are summarized in the table below:

(b) (4)

(b) (4)

Reviewer's comment:

I reviewed the amendment 13 received on Nov. 30, 2018 which contains EM data covering the period when the PPQ batches were manufactured. As the data indicated all EM results during the PPQ campaign conform to acceptance criteria.

H. Shipping of DS

(b) (4)



Reviewer's comment:

There is no defined maximum shipping time, the shipping validation appears acceptable. The shipping validation was reviewed extensively during the PLI, and this issue was discussed with the firm and as one of the discussion items. See EIR for details.

I. Stability for DS

The stability design for studies conducted on CYD dengue Drug Substances is presented in the following tables

(b) (4)

J. Overall Process Validation Conclusion

As a conclusion for (b) (4) consecutive batches of CYD dengue Drug Substances, all validation acceptance criteria are met and demonstrate the reproducibility of the production process for each of the following manufacturing process stages:

(b) (4)

The validation studies performed show that:

- The manufacturing process is under control as all CPPs comply with their ranges or limits, and are monitored at their target values (except for one CPP but only due to an equipment failure);
- The product quality is achieved as all results for release and IPC tests meet the acceptance criteria;
- (b) (4) characteristics are satisfactory;
- Consistency of production is confirmed as (b) (4) results are similar for each serotype batches.

Additionally, validation data also demonstrate that process performance with regards to virus concentration yields and impurities removal is reproducible and that process biocontamination is under control.

Reviewer's comment:

(b) (4) steps, results met specifications. There were deviations for (b) (4) samples with over the limit, and the roots cause was a (b) (4). This deviation was also reviewed during the PLI. See EIR for additional details. Review of other IPC and release tests are deferred to product office.

V. DRUG PRODUCT (CYD DENGAXIA)

1. FACILITY

Phase I and Phase II ((b) (4)) were manufactured at the Sanofi Swiftwater facility and starting from Phase III ((b) (4)), the bulk drug product (BDP) was manufactured in Sanofi ((b) (4)) at a larger scale and with a new FBP stabilizing solution for virus stability during lyophilization process.

The CYD Dengvaxia drug product (DP) is now manufactured at the Sanofi Pasteur ((b) (4)) using bulk DS manufactured at Sanofi ((b) (4)) facility in ((b) (4)), located at ((b) (4)). The site has no prior FDA inspection history, and a PLI was conducted by CBER from ((b) (4)). See EIR for details related to the PLI. The activities at ((b) (4)) are as the follows:

Table 39: Location of the CYD Dengue Vaccine Manufacturing Steps

Manufacturing Step	Location
Final Bulk Production	(b) (4)
Filling	
Freeze-Drying	
Cap crimping	
Capped filled product vials storage before inspection	
Visual vials inspection	
Personnel locker rooms	

The labeling and the secondary packaging of the CYD dengue vaccine is performed at the Swiftwater PA site, in the United States.

The main CYD dengue vaccine activities are performed in building ((b) (4)). Rooms/area of buildings ((b) (4)) are identified for additional activities such as visual inspection, storage, personnel locker rooms. Building ((b) (4)) is located at ((b) (4)) site and its whole surface of the building ((b) (4)) is ((b) (4)). Building ((b) (4)) is a ((b) (4)) floor manufacturing facility:

((b) (4))

(b) (4)

There are other products that share the manufacturing areas with Dengvaxia as described below.

Table 40: Additional Activities performed in Building (b) (4)

Product	Activity	Location
Combined Purified Vi Polysaccharide Typhoid and Inactivated Hepatitis A Vaccine (HA/Vi vaccine)	<i>Formulation</i>	(b) (4)
	<i>Filling and Capping</i>	
	<i>Inspection</i>	
Oral Poliomyelitis vaccines	<i>Formulation</i>	
	<i>Filling</i>	
	<i>Capping</i>	
	<i>Inspection</i>	
<i>Haemophilus</i> type b conjugate vaccine	<i>Formulation</i>	

Product	Activity	Location
Yellow fever vaccine	<i>Filling</i>	(b) (4)
	<i>Capping</i>	
	<i>Inspection</i>	

These product share with Dengvaxia production in the formulation, filling, lyophilization, capping and inspection areas as indicated in the bolded locations. The production areas are dedicated on production campaign bases, and no two products are processed at the same time in these areas. Appropriate procedures are in place to prevent potential cross contamination between different products, personnel and Drug Substances. Line clearance procedures are in place between product changes.

Decontamination of the filling suite


(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

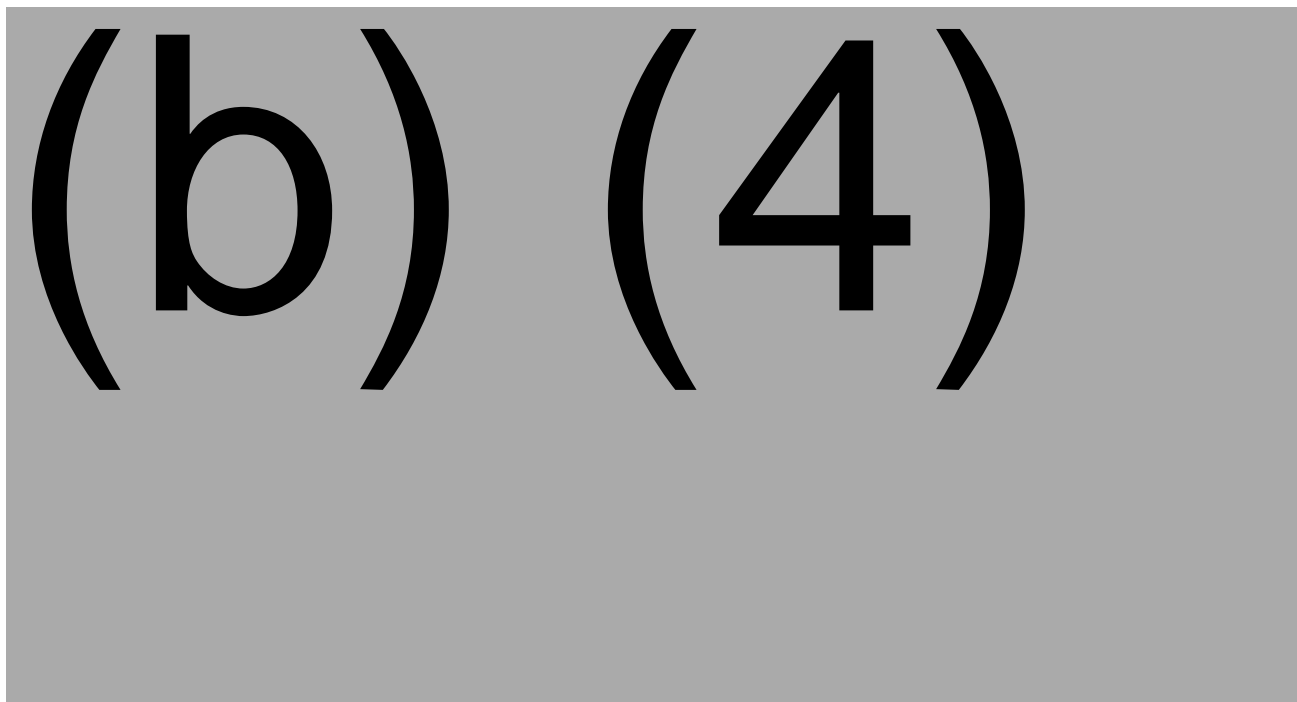
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Reviewer's comment:

I reviewed the layout, material flow, equipment flow, personnel flow, product flow and waste flow of the facility, and also the decontamination with (b) (4) for the filling area, they appear adequate. The facility is reviewed in detail during the PLI. See (b) (4) EIR for more details.

2. DENG VAXIA DP MANUFACTURING PROCESS

A flow diagram detailing the steps of the FBP manufacturing process for CYD dengue vaccine is shown below in Figure 7:



(b) (4)

3. EQUIPMENT for DENG VAXIA DP MANUFACTURING

Major process equipment used in building (b) (4) for the manufacture of CYD dengue vaccine is described in the Table below:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Sterilization Validation for the Lyophilizers

The (b) (4) lyophilizers are (b) (4) by (b) (4) immediately after (b) (4). The (b) (4) parameters for the lyophilizers are listed in the table below:

4. DRUG PRODUCT MANUFACTURING PROCESS VALIDATION

The overall process validation for the production of CYD dengue vaccine assesses the major steps to ensure adequate quality assurance of the drug product. The process validation for the production of CYD dengue vaccine took place in two following steps: Initial validation and a complementary validation with the implementation of (b) (4) sterile filtration after formulation and before filling. The process validation covering the manufacturing steps and parameters studied for CYD dengue vaccine are listed in the following Table 63.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

G. Crimping

The crimping machine is used post lyophilization to seal the stoppers on the DP vials. The BLA submission stated that the crimping machine and process have been qualified, but during the PLI, it was noted that the crimping process has not been validated for Dengvaxia production, and an FDA 483 was issued to this issue. See (b) (4) EIR for details.

5. CCIT

The vaccine DP container closure systems consist of single-dose 3 mL glass vial with a stopper and a cap. The (b) (4) 3 mL (b) (4) glass vial is closed with (b) (4) 13 mm latex free butyl rubber (b) (4) stopper and is sealed with a (b) (4) 13 mm (b) (4) aluminum with flip-off crimp seal. Cleaning and depyrogenation of the 3 mL vials were reviewed in the equipment qualification sections.

The CCIT for the DP was not provided in the initial BLA, and Sanofi provided the CCIT information in Amendment 13 received on November 30, 2018. All DP vials off the lyophilization and after defined minimum storage time receive a 100% non-destructive inspection to measure (b) (4). The (b) (4) CCIT machine was qualified for testing the 3 mL vials used for Dengvaxia DP by detecting (b) (4) defective vials concealed among (b) (4) test vials. The machine runs at (b) (4) and vial leak specification is at (b) (4). It was determined that sealed vial requires (b) (4) to obtain a (b) (4) under the leak test condition, so firm selected to conduct the 100% CCIT for all lyophilized vials after (b) (4) of storage to ensure sufficient time is provided for potential leaks to be detected. This method is sensitive in detecting a leak in the size as small as (b) (4). CCIT was extensively reviewed during the PLI. See (b) (4) EIR for more details.

6. VISUAL INSPECTION

100% visual inspection (container and product appearance) is done off the lyophilization and capping process. An automatic inspection machine and a manual visual inspection bench are installed in room (b) (4). (b) (4) inspection machines and a manual visual inspection bench are located in room (b) (4). Vials rejected by the automatic inspection machine will be inspected by operators on the (b) (4) inspection station. Manual visual inspection could also be performed. Visual inspection was reviewed during PLI, see (b) (4) EIR for details.

7. STORAGE AND TRANSPORTATION

The commercial DP batches storage condition in this BLA is validated to be at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ which is different from the (b) (4) used in phase I study. The transportation from Sanofi (b) (4) to Sanofi SWR of CYD dengue vaccine in the primary packaging is performed either by (b) (4), at temperature between $+2^{\circ}\text{C}$ and $+8^{\circ}\text{C}$. At (b) (4) site, the unlabeled vial containing the freeze-dried product is packaged and loaded into active container with a set temperature at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. After receipt at Swiftwater site, the freeze-dried product is then labelled and co-packaged with the diluent before to be shipped under controlled conditions to the distribution centers. Sanofi conducted simulated shipping validations using commercial batch sized (up to ~ (b) (4)) vials filled with media and placeable. The DP shipping validation was extensively reviewed during PLI, there was no major objectionable issue for the shipping validation. See (b) (4) EIR for more details.

8. STABILITY SUMMARY AND CONCLUSIONS

Initial stability studies were performed in order to assess the stability of Drug Product issued from Drug Substances manufactured at (b) (4) site and to support the shelf-life of 36 months at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

Then a new stability study was initiated on the Drug Product issued from Drug Substances manufactured at (b) (4) site in the frame of the manufacturing process transfer of CYD dengue DS from (b) (4) site (Building (b) (4)) to (b) (4) site (Building (b) (4)).

This stability study was performed on (b) (4) industrial batches to confirm the shelf-life of 36 months at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. This study also aims at assessing the stability of the vaccine under accelerated storage conditions at (b) (4) to support possible cold chain break. The period applied at (b) (4) observed during the previous studies carried out up to (b) (4). Furthermore, the stability study on the reconstituted product is performed for each batch of CYD dengue vaccine over a period of (b) (4) under normal storage conditions ($+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$).

Table 88: Tests Performed on the Drug Product during Stability Study at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$

Test	Acceptance criteria	Stability time-points (months)
Appearance of the freeze-dried product	White homogeneous freeze-dried product with possible retraction at the basis (ring-shaped cake possible)	T0-3-6-9-12-18-24-36 months
Appearance after dissolution	Colorless limpid solution with possible presence of white to translucent particles (of endogenous nature)	T0-3-6-9-12-18-24-36 months
Dissolution time	(b) (4)	T0-3-6-9-12-18-24-36 months
(b) (4)	(b) (4)	T0-3-6-9-12-18-24-36 months
Residual moisture	(b) (4)	T0-3-6-9-12-18-24-36 months
(b) (4)	(b) (4)	T0-36 months
Bacterial and fungal sterility test	No bacterial and fungal growth	T0-36 months
Virus concentration (CCID₅₀)	(b) (4) log ₁₀ CCID ₅₀ /dose for each serotype and (b) (4) log ₁₀ CCID ₅₀ /dose for each serotype	T0-3-6-9-12-18-24-36 months
(b) (4)	(b) (4)	T0-18-36 months
Abnormal toxicity test*	No sign of illness or death within 14 days after inoculation	T0-36 months
Container closure integrity test	Absence of leak	T0-12-24-36 months

* This test will be no longer included in the stability studies as it is not a stability indicating testing.

(b) (4)

(b) (4)

Table 91: Tests Performed during the Stability Study at +5°C ± 3°C on Reconstituted Product

Test	Acceptance criteria	Stability time-points (hours)	
		Samples at T0	Samples stored after 36 months
Appearance after dissolution	Colorless limpid solution with possible presence of white to translucent particles (of endogenous nature)	0- (b) (4) hours after reconstitution	0- (b) (4) hours after reconstitution
(b) (4)	(b) (4)	0- (b) (4) hours after reconstitution	0- (b) (4) hours after reconstitution
Virus concentration	(b) (4) log ₁₀ CCID ₅₀ /dose for each serotype and (b) (4) log ₁₀ CCID ₅₀ /dose for each serotype	0- (b) (4) hours after reconstitution	0- (b) (4) hours after reconstitution

Bioburden and CCIT are part of the stability tests performed for all samples.

Reviewer's comment

All the results from IPC and final release tests for the PPQ batches analyzed from the validation study appear to meet the acceptance criteria and the data from these PPQ batches shows the manufacturing process consistency among the (b) (4) PPQ batches. The available bioburden and CCIT data all met acceptance criteria. Review of other IPC and final release test data is deferred to product office

VII. DILUENT

The diluent is part of the final Drug Product co-packaged with lyophilized Dengvaxia vaccine. It is a 0.4% Sodium Chloride solution in a unit dose presentation in 2 mL glass vial filled to 0.5 mL with no preservative used as a diluent for the reconstitution of freeze-dried vaccines. The diluent is a clear, colorless liquid that is devoid of foreign matter. The composition of the diluent is described in the Table 92 below:

Table 92: Composition of Drug Product

Component	Amount on a per Unit Basis	Function	Reference to Quality Standards
Sodium chloride	2.0 mg	Excipient	(b) (4)
Water for injection	0.5 mL	Excipient	(b) (4)

1. DILUENT MANUFACTURE FACILITY

The diluent is manufactured in Building (b) (4) at Sanofi Pasteur Inc. Swiftwater, Pennsylvania facility. This is a multi-product facility, and the products manufacture at this facility is listed in the Table below:

Table 93: Building (b) (4) Licensed Product Listing

Product	Dose size	Formulation Skid #	Filling Line
Influenza Virus Vaccines	1 dose syringe	(b) (4)	(4)
	1 dose vial		
	10 dose vial		
Meningococcal (Groups A,C,Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine [Menactra®]	1 dose vial		
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed [Daptacel®]	1 dose vial		
Tetanus and Diphtheria Toxoids Adsorbed [Tenivac®]	1 dose syringe		
	1 dose vial		
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed [Adacel®]	1 dose syringe		
	1 dose vial		
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Meningococcal Outer Membrane Protein Complex), and Hepatitis B (Recombinant) Vaccine [Vaxelis®]	1 dose syringe		

Product	Dose size	Formulation Skid #	Filling Line
Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine [Quadracel®]	1 dose vial	(b) (4)	(4)
Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine [Pentacel®]	1 dose vial		
Alirocumab 75mg/mL [Praluent®]	1 dose syringe		
Diluent for Reconstitution of Yellow Fever Vaccine [YF-VAX®]	1 dose vial 10 dose vial		
Diluent for Reconstitution of Haemophilus b Conjugate Vaccine [ActHIB®]	1 dose vial		

The formulation, filling and inspection process in (b) (4) for the Diluent Drug Product utilizes the Buffer Preparation areas and Filling Line (b) (4) which it shares with other licensed diluents utilizing the same rooms / equipment in (b) (4); licensed products filled on the syringe filling lines (Lines (b) (4)) are in the same facility but do not use the same rooms/equipment.

2. DILUENT MANUFACTURING EQUIPMENT

The equipment in Building (b) (4) used for diluent manufacturing are listed in the Table below:

Table 94: System / Equipment for Building (b) (4)

(b) (4)

IQ/OQ/PQ were conducted for major equipment and cleaning/sterilization validations have also been conducted for (b) (4) filling line.

3. DILUENT MANUFACTURING PROCESS VALIDATION

The 0.4% NaCl diluent is formulated from sodium chloride and water for injection.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

C. Process validation

The process validation covered (b) (4) aspects of the manufacturing process including: (b) (4)

Aseptic Process Simulation (APS, media fill)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Process validation batches

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

D. Stability

BLA provided summary report for (b) (4) stability studies, including (b) (4) for filled final product in vials. The hold time for the Bulk Diluent is validated for (b) (4). The Final Container Unit Dose Diluent filled in Building (b) (4), is stored at (b) (4) at the unlabeled stage.

Once labeled and co-packaged, the current licensed storage temperature of the labeled Final Container Unit Dose Diluent is 2°C to 8°C. The hold time for the Final Container Unit Dose Diluent is validated up to twenty-four (24) months from the date of filling.

Product sterility and container closure integrity are demonstrated through the stability programs with the final 24 month sterility data.

E. CCIT for Diluent

Container Closure System

The unit dose diluent is supplied in a (b) (4) formed (b) (4) 2 mL (b) (4) borosilicate glass vial with a 13 mm finish, blow-back, flat bottom. The stopper is a 13 mm butyl latex free stopper. The vial and stopper are fitted with a 13 mm aluminum (or equivalent) seal and a polypropylene flip-off button. The stoppers are tested by the vendor for (b) (4) via the (b) (4) test and the (b) (4) test. Leachable screening testing was conducted to identify and provide semi-quantitative estimation of any potential leachable compound from the latex-free stopper or glass vial when in contact with the sodium chloride diluent. Stability studies have been completed on batches of the Drug Product, 0.4% Sodium Chloride Diluent. Available results comply with the acceptance criteria, showing absence of interaction of potential leachable from the packaging materials with the Drug Product.

CCIT

The dynamic challenge included a (b) (4)

The determined sensitivity is (b) (4). The results for CCIT are summarized in the table below:

Table 103: CCIT Sample Collection and Summary of Test Results

(b)	(4)
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Reviewer's comment:

Sanofi did not use positive controls with defect or breach, instead, they used spiked vials with very low (b) (4). Although not ideal for the CCIT test not using any positive controls with defect to demonstrate the ability to detect actual breach of the seal, the (b) (4) sensitivity provides acceptable assurance for this method. In the stability study, sterility is used as final release test for the diluent at 24 month which is the current shelf life for the diluent. In addition, the diluent with exactly the same contents and container closure is also licensed for use with ActHIB® (refer to STN 103935/5376, approved in June 2016). Considering the information collectively, the assurance for container closure integrity is acceptable.

VII. REVIEW ISSUES AND CONCLUSION

Based on the data I reviewed in this BLA, supplements submissions and pre-license inspections for the DS and DP manufacturing facilities, I recommend approval of this BLA.