Summary Basis for Regulatory Action

Date: May 1, 2019

From: Kirk Prutzman, Ph.D., Chair of the Review Committee

BLA STN#: 125682/0

Applicant Name: Sanofi Pasteur Inc.

Date of Submission: August 31, 2018

Goal Date: May 1, 2019

Proprietary Name: DENGVAXIA

Established Name: Dengue Tetravalent Vaccine, Live

Indication: DENGVAXIA is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. DENGVAXIA is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

Limitations of use:

- DENGVAXIA is not approved for use in individuals not previously infected by any dengue virus serotype or for whom this information is unknown. Those not previously infected are at increased risk for severe dengue disease when vaccinated and subsequently infected with dengue virus. Previous dengue infection can be assessed through a medical record of a previous laboratory-confirmed dengue infection or through serological testing prior to vaccination.

- The safety and effectiveness of DENGVAXIA have not been established in individuals living in dengue non-endemic areas who travel to dengue endemic areas.

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

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

X I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the Summary Basis of Regulatory Action (SBRA).

Document title	**Reviewer name, Document date**
CMC Reviews • *CMC (OVRR/DVP)* • *Inspection waiver memo (OCBQ/DMPQ)* • *Facilities review (OCBQ/DMPQ)*	Dino Feigelstock, Ph.D. (CMC Reviewer OVRR/DVP) – May 1, 2019 Jie He (Inspection waiver memo, OCBQ/DMPQ) April 3, 2019; Jie He (Facilities review, OCBQ/DMPQ) – April 30, 2019
Clinical Reviews • *Clinical (OVRR/DVRPA)* • *Postmarketing safety epidemiological review (OBE/DE)* • *Benefit/Risk Review (OBE)* • *BIMO (OCBQ/DIS)*	Ralph LeBlanc, M.D., Ph.D. (Clinical, OVRR/DVRPA) - May 1, 2019 Wambui Chege, Ph.D. (OBE/DE) - May 1, 2019 Hong Yang, Ph.D. (OBE) - April 8, 2019 Christine Drabick, Malcolm Nasirah (OCBQ/DIS) - April 3, 2019
Statistical Reviews • *Clinical efficacy data (OBE/DB)* • *Clinical safety data (OBE/DB)* • *Non-clinical data (OBE/DB)*	Mridul Chowdhury, Ph.D. (OBE/DB) –April 30, 2019 Lei Huang, Ph.D. (OBE/DB) – April 30, 2019 Lei Huang, Ph.D. (OBE/DB) – April 30, 2019
Pharmacology/Toxicology Reviews • *Toxicology (OVRR/DVRPA)* • *Developmental toxicology (OVRR/DVRPA)* • *Animal pharmacology (OVRR/DVP)*	Nabil Al-Humadi, Ph.D., (OVRR/DVRPA) – April 11, 2019 Claudia Wrzesinski, DVM, Ph.D., (OVRR/DVRPA) – April 11, 2019 Dino Feigelstock, Ph.D. (CMC Reviewer OVRR/DVP) - May 1, 2019
Labeling Reviews • *APLB (OCBQ/APLB)* • *Others*	Oluchi Elekwachi, PharmD, M.P.H. (PNR Memo, OCBQ/APLB) – September 27, 2018 Oluchi Elekwachi, PharmD, M.P.H. (Labeling review, OCBQ/APLB) – April 12, 2019 Ramachandra Naik, Ph.D. (Labeling review, OVRR/DVRPA) - May 1, 2019
Other Reviews • *Analytical methods and product testing*	Simleen Kaur, M.Sc. (OCBQ/DBSQC) – November 20, 2018Tao Pan, Ph.D. (OCBQ/DBSQC) – April 16, 2019

Document title	Reviewer name, Document date
Other Reviews • *Analytical methods and product testing*	Noel Baichoo, Ph.D. (OCBQ/DBSQC) – April 22, 2019 Marie Anderson (OCBQ/DBSQC) - May 1, 2019
Advisory Committee Meeting	March 7, 2019

1. INTRODUCTION

Sanofi Pasteur Inc. (SP) submitted Biologics License Application (BLA) 125682 for licensure of Dengue Tetravalent Vaccine, Live. The proprietary name of the vaccine is DENGVAXIA. DENGVAXIA is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. The vaccine is administered subcutaneously (SC) in three doses (0.5 mL each) at six-month intervals (months 0, 6, and 12).

DENGVAXIA is a live, attenuated virus vaccine consisting of four chimeric yellow fever dengue (CYD) viruses (one CYD virus each corresponding to dengue serotypes 1, 2, 3, and 4). Each of the four CYD viruses (CYD-1, CYD-2, CYD-3, and CYD-4) in DENGVAXIA was constructed using recombinant DNA technology by replacing the sequences encoding the pre-membrane (prM) and envelope (E) proteins in the yellow fever (YF) 17D204 vaccine virus genome with those encoding the homologous prM and E gene sequences of dengue virus serotypes 1, 2, 3, or 4. Each CYD virus is cultured separately in Vero cells (African Green Monkey kidney) under serum-free conditions, harvested from the supernatant of the Vero cells and purified and concentrated by membrane chromatography and ultrafiltration. The purified and concentrated harvest of each CYD virus is then diluted in a stabilizer solution and (b) (4) to produce each of the four monovalent CYD virus drug substances. The CYD virus drug substances can be stored at (b) (4). To manufacture the final drug product, the four monovalent drug substances are mixed with stabilizer solution, filtered, filled into vials and freeze-dried.

DENGVAXIA is supplied in a single dose configuration that contains one vial of lyophilized vaccine antigen and one vial of saline diluent. The lyophilized vaccine antigen must be reconstituted with the saline diluent to form DENGVAXIA before use. After reconstitution, each 0.5 mL dose contains 4.5 - 6.0 $\log_{10}$ $CCID_{50}$ (50% Cell Culture Infectious Dose) of each of the CYD viruses. Each 0.5 mL dose is formulated to also contain 2 mg sodium chloride and the following ingredients as stabilizers: 0.56 mg essential amino acids (including L-phenylalanine), 0.2 mg non-essential amino acids, 2.5 mg L-arginine hydrochloride, 18.75 mg sucrose, 13.75 mg D-trehalose dihydrate, 9.38 mg D-sorbitol, 0.18 mg trometamol, and 0.63 mg urea. DENGVAXIA does not contain preservative.

The dating period for the lyophilized vaccine antigen is 36 months from the date of manufacture when stored at 2-8° C. The date of manufacture shall be defined as the

date of lyophilization of the filled final bulk product. The dating period for each of the four monovalent CYD virus drug substances shall be (b) (4) . The dating period for the saline diluent is 24 months from the date of manufacture when stored at 2-8° C. The date of manufacture is defined as the date of filling of the diluent. The expiration date for the packaged product, consisting of lyophilized vaccine antigen plus saline diluent, shall be dependent on the shorter expiration date of either component.

DENGVAXIA Indication

Sanofi Pasteur submitted their original BLA for DENGVAXIA requesting an indication for 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. The proposed indication was based on clinical efficacy data in subjects 9 through 16 years of age. Efficacy in individuals aged 17 through 45 years of age was proposed to be based on immunogenicity data from studies conducted in Vietnam and India. These data were discussed at the March 7, 2019, Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting (see Section 8). The committee expressed concern about inferring vaccine effectiveness in the adult population based on efficacy in pediatric trials and antibody titers in adults because the available adult data were derived from small immunogenicity studies and conducted in countries with high dengue endemicity. There was concern that these data may not reflect immune responses to DENGVAXIA in adults living in Puerto Rico, which is the most populated dengue endemic area in the United States (U.S.) and will likely have the majority of DENGVAXIA use in the U.S. (see Background). Some committee members opined that in the absence of immunogenicity data relevant to previous dengue exposure of adults living in Puerto Rico, it would be difficult to infer effectiveness in the adult population. These concerns were discussed between Sanofi Pasteur and CBER after the March 7, 2019, VRPBAC meeting. Both CBER and Sanofi Pasteur agreed that additional studies relevant to the adult population in Puerto Rico could support inclusion of individuals 17 through 45 years of age in the indication. Sanofi Pasteur informed CBER that they decided for this BLA submission to pursue an indication only for individuals 9 through 16 years of age and requested a revised indication that does not include individuals 17 through 45 years of age.

2. BACKGROUND

Dengue disease is an acute, systemic viral infection caused by four closely related but antigenically distinct virus serotypes (1, 2, 3, and 4) transmitted primarily by the *Aedes aegypti* mosquito (1). Primary infection is most commonly asymptomatic or can cause a flu like illness (dengue fever), both of which typically result in long-lasting immunity against the infecting serotype and transient cross-protection against heterotypic infection. However, waning heterotypic immunity is associated with an increased risk of potentially lethal complication with secondary infection called severe dengue (including dengue hemorrhagic fever/dengue shock syndrome [DHF/DSS]). Annually, an estimated 390 million dengue infections occur worldwide, of which approximately 100

million are associated with clinical manifestations; 500,000 with hospitalization; and 20,000 with death (2).

Dengue disease is a major public health concern in more than 128 countries. It is endemic in Asia, the Pacific area, Africa, and Latin America (including the Caribbean), with the four dengue virus serotypes found in tropical and sub-tropical regions, including some European territories (3). Dengue is endemic in the U.S. territories of Puerto Rico, Guam, Samoa, and the U.S. Virgin Islands (4).

Puerto Rico has experienced epidemic dengue activity periodically since 1963. Dengue continues to be endemic in Puerto Rico, with three to nine thousand suspected dengue cases reported during non-outbreak years. Since 1990, there have been four large epidemics of dengue. In 1994 there were 24,700 suspected dengue cases reported, in 1998 there were 17,000 cases reported, and in 2007 there were 10,508 cases reported. More recently in 2010, 26,766 cases of suspected dengue infections were reported (5).

Nearly all dengue cases reported in the 48 continental U.S. were acquired elsewhere by travelers or immigrants (6,7). These imported cases rarely result in secondary transmission because contact between *Aedes* and people is infrequent in the continental U.S. The last reported continental dengue outbreak was in south Texas in 2005 (8). A small dengue outbreak occurred in Hawaii in 2001 (9).

In the U.S., there are no licensed vaccines or anti-viral drugs for the prevention or treatment of dengue. Management of dengue disease is limited to supportive care with rest, control of fever and pain with antipyretics and analgesics, and adequate fluid intake. Management of severe dengue disease includes intensive supportive care and fluid management. Preventive measures are limited to mosquito vector control and personal protection measures.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Manufacturing Overview

DENGVAXIA is a live, attenuated, tetravalent, chimeric virus vaccine containing the replication genes and the capsid gene from the attenuated Yellow Fever [17D] virus and the Pre-M and ENV genes from each of the four dengue serotypes (CYD Virus). DENGVAXIA consists of the lyophilized vaccine antigen and saline diluent. The saline diluent is used to reconstitute the lyophilized vaccine antigen prior to administration. Manufacture of the lyophilized vaccine antigen drug substance takes place in (b) (4) . The final formulated drug product will be manufactured, filled, and lyophilized in (b) (4) . The saline diluent will be manufactured and filled in Swiftwater, Pennsylvania. Labeling and packaging operations for both the lyophilized vaccine antigen vial and the saline diluent vial are conducted in Swiftwater, Pennsylvania.

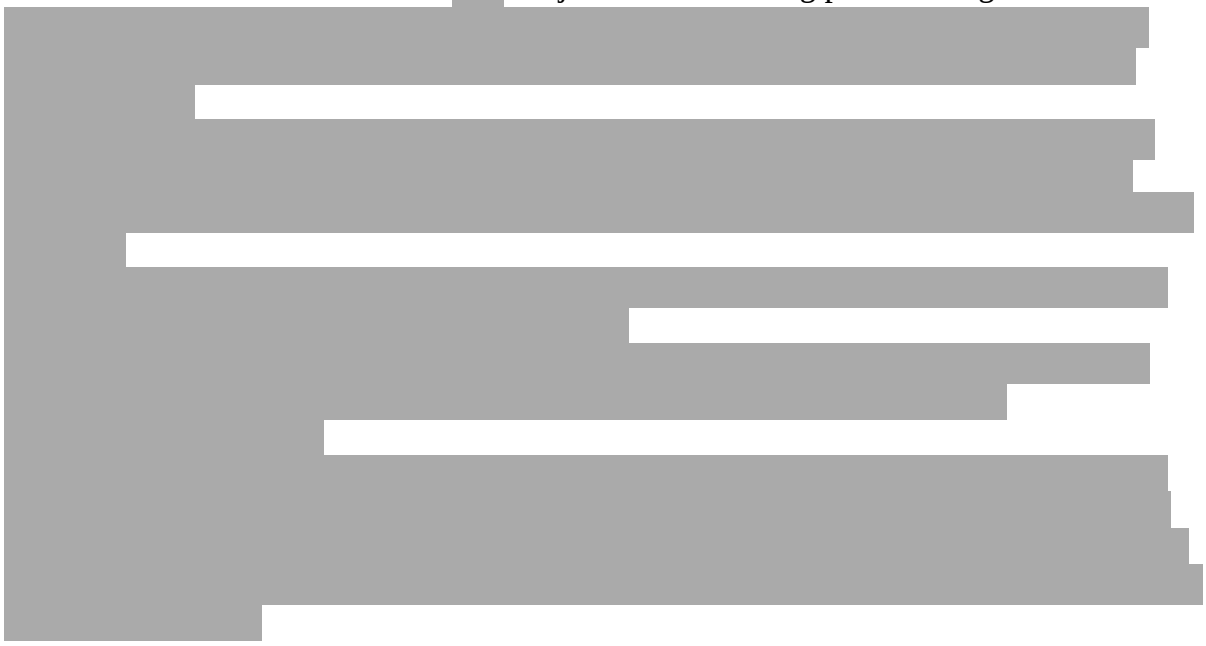
Lyophilized Vaccine Antigen of DENGVAXIA

The lyophilized vaccine antigen contains four live-attenuated chimeric dengue viruses (serotypes 1, 2, 3, and 4). Each monovalent CYD virus was obtained separately via recombinant DNA technology. The four CYD viruses were constructed by replacing the genes encoding the pre-membrane (prM) and envelope (E) proteins of the structural proteins in the attenuated yellow fever (YF) 17D virus genome (the strain contained in the yellow fever vaccine) with the corresponding gene of one of the four wild type dengue serotypes 1, 2, 3 and 4.

Lyophilized Vaccine Antigen Drug Substances (DS)

The manufacture of lyophilized vaccine antigen Drug Substances is the same for each of the four viruses and is divided into (b) (4) major manufacturing process stages:

(b) (4)



Lyophilized Vaccine Antigen Drug Product (DP)

The manufacturing process of the lyophilized vaccine antigen Drug Product is divided into the following critical steps:

(b) (4)

Composition

The composition of the lyophilized vaccine antigen of DENGVAXIA and the function of the ingredients are provided in Table 1.

Table 1. Composition of the Lyophilized Vaccine Antigen of DENGVAXIA

Ingredients	Quantity (per 0.5 mL dose)	Function
(b) (4)		

(b) (4)

Specifications and Methods

The tests and specifications applied for routine release of the lyophilized vaccine antigen are shown in Table 2.

Table 2. Control of the Lyophilized Vaccine Antigen: Tests and Specifications

Test	Acceptance criteria
Appearance of the freeze-dried product	White homogeneous freeze-dried product with possible retraction at the basis (ring-shaped cake possible)
Appearance after dissolution	Colorless limpid solution with possible presence of white to translucent particles (of endogenous nature)
Dissolution time	(b) (4)
(b) (4)	(b) (4)
Residual moisture	(b) (4)
(b) (4)	(b) (4)
Bacterial and fungal sterility test	No bacterial and fungal growth
Virus concentration ($CCID_{50}$)	(b) (4) $CCID_{50}$/dose for each serotype and (b) (4) $CCID_{50}$/dose for each serotype
(b) (4)	(b) (4)
Abnormal toxicity test	No sign of illness or death within (b) (4) after inoculation
Container closure integrity test	Absence of leak

$CCID_{50}$: 50% Cell Culture Infectious Dose **NMT:** Not More Than **NLT:** Not Less Than

Stability

For the long-term storage condition study, parameters monitored are Appearance of the freeze-dried product, Appearance after dissolution, Dissolution time, (b) (4), Residual moisture, (b) (4), Bacterial and fungal sterility test, CYD Vaccine potency by $CCID_{50}$, (b) (4) Abnormal toxicity test, and Container closure integrity test. The tests selected to monitor the accelerated stability studies are (b) (4) The stability data provided in the submission support a dating period of 36 months from the date of manufacture (i.e., date of lyophilization) when stored at 2-8 °C for the DENGVAXIA antigen lots filled in (b) (4) 3 mL (b) (4) glass vials.

The Saline Diluent of DENGVAXIA

Composition

The composition of the saline diluent and the function of the ingredients are provided in Table 3.

Table 3. Composition of the Saline Diluent

Ingredients	Quantity (per 0.5 mL dose)	Function
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.0 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	0.5 mL	Excipient

UNII: Unique Ingredient Identifier

Manufacturing

Overall, the manufacturing process of the saline diluent consists of the following steps:

- Formulation of the saline diluent: Sodium Chloride and Water for Injection are mixed, (b) (4) is adjusted if applicable, and samples are tested for (b) (4).
- (b) (4)
- Filling into (b) (4) 2 mL (b) (4) borosilicate glass vials performed under aseptic conditions.

Specifications and Methods

The tests and specifications applied for routine release of the saline diluent of DENGVAXIA are presented in Table 4.

Table 4. Control of Saline Diluent: Tests and Specifications

Test	Acceptance criteria
Color	Colorless
Odor	Odorless
Appearance	Clear solution, No foreign matter
Sodium Identity	Conforms
Chloride Identity	Conforms
Sodium Chloride	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Vial Volume	NLT 0.6 mL/vial
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Particulate Matter	(b) (4)
Sterility	No Growth
Bacterial Endotoxin Test ((b) (4))	(b) (4)

Test	Acceptance criteria
Safety	1. Animal survived test period 2. No nonspecific or unexpected responses observed 3. Final animals weights no less than starting weights
Major A Defects	No Critical Defects Major Defects AQL: (b) (4) Minor Defects AQL: (b) (4)
Major B Defects	(b) (4)
Container Closure Integrity Test	Container Closure Integrity Maintained

NMT: Not More Than
NLT: Not Less Than
(b) (4)
(b) (4)
AQL: Acceptable Quality Limit

Stability

For the long-term storage condition study of saline diluent filled in 2 mL glass (b) (4) borosilicate glass vials, parameters monitored are Appearance, Sodium and chloride, (b) (4), Sterility, and Container Closure Integrity Test. The stability data provided in the submission support a dating period of 24 months from the date of manufacture (i.e., filling date) when stored at 2-8 °C for the saline diluent lots filled in 2 mL glass (b) (4) borosilicate glass vials with 13 mm latex-free stoppers.

The DENGVAXIA Vaccine

Product Composition

As previously described, DENGVAXIA consists of one vial of lyophilized vaccine antigen that is reconstituted at the time of use with 0.6 mL of liquid from the accompanying vial of saline diluent. A single dose of DENGVAXIA is 0.5 mL, and it does not contain preservative. The composition of the reconstituted vaccine and the function of the ingredients are provided in Table 5.

Table 5. Composition of the DENGVAXIA Vaccine

Ingredients	Quantity (per 0.5 mL dose)	Function
CYD VIRUS SEROTYPE 1 LIVE (UNII: 75KB2HPX5H)	4.5 - 6.0 $\log_{10}$ $CCID_{50}$/dose	Active Ingredient
CYD VIRUS SEROTYPE 2 LIVE (UNII: FH5SVG7GLC)	4.5 - 6.0 $\log_{10}$ $CCID_{50}$/dose	Active Ingredient
CYD VIRUS SEROTYPE 3 LIVE (UNII: RHT2Q37FYG)	4.5 - 6.0 $\log_{10}$ $CCID_{50}$/dose	Active Ingredient
CYD VIRUS SEROTYPE 4 LIVE (UNII: RS26HP5ND2)	4.5 - 6.0 $\log_{10}$ $CCID_{50}$/dose	Active Ingredient
AMINO ACIDS, ESSENTIAL (UNII: N7U7BXP2OI)	0.56 mg	Stabilizer
AMINO ACIDS, NON-ESSENTIAL (UNII: 0O72R8RF8A)	0.2 mg	Stabilizer
ARGININE HYDROCHLORIDE (UNII: F7LTH1E20Y)	2.5 mg	Stabilizer
SUCROSE (UNII: C151H8M554)	18.75 mg	Stabilizer
TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)	13.75 mg	Stabilizer
SORBITOL (UNII: 506T60A25R)	9.38 mg	Stabilizer
TROMETHAMINE (UNII: 023C2WHX2V)	0.18 mg	Stabilizer
UREA (UNII: 8W8T17847W)	0.6 mg	Stabilizer
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2 mg	Excipient

$CCID_{50}$: 50% Cell Culture Infectious Dose.
UNII: Unique Ingredient Identifier

Presentation and Packaging System

DENGVAXIA is supplied as two vials co-packaged in a carton. Each carton contains one single-dose vial of lyophilized vaccine antigen and one single-dose vial of the saline diluent.

Container Closure System

As mentioned above, DENGVAXIA is supplied as a lyophilized vaccine antigen vial and a saline diluent vial. The lyophilized vaccine antigen container closure system consists of a single-dose (b) (4) 3 mL glass vial with a (b) (4) 13 mm latex free butyl rubber (b) (4) stopper and a (b) (4) 13 mm (b) (4) aluminum cap with flip-off crimp seal. Sanofi conducted the container closure integrity testing of the lyophilized vaccine antigen at its (b) (4) facility in (b) (4), employing the (b) (4) test method; all acceptance criteria were met.

The saline diluent container closure system is a single-dose (b) (4) 2 mL (b) (4) borosilicate glass vial with a 13 mm finish, blow-back, flat bottom, closed with a 13 mm butyl latex free stopper and sealed with a 13 mm aluminum cap with polypropylene flip-off seal. Sanofi conducted the container closure integrity testing of the saline diluent at its Swiftwater facility in PA, employing the (b) (4) test method; all acceptance criteria were met.

Stability

Sanofi Pasteur conducted in-use stability studies to support the maximum temperature and time period that the reconstituted vaccine can retain its physicochemical properties. The tests used to monitor the stability of the reconstituted vaccine are: Appearance, (b) (4), and CYD Vaccine potency by $CCID_{50}$. Based on the data generated, DENGVAXIA, once reconstituted, retains its quality attributes for up to 30 minutes at 2-8 °C (36-46 °F).

The carton labels and the Prescribing Information (PI) state that after reconstitution, DENGVAXIA should be administered immediately or stored refrigerated between 2-8 °C (36-46 °F) and used within 30 minutes. The reconstituted vaccine should be discarded if not used within 30 minutes.

Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the DENGVAXIA drug substances and drug product were found to be adequate for their intended uses.

Comparability Protocols (CPs)

Sanofi Pasteur submitted the following CPs in the BLA:

- (b) (4) reference standard used in the (b) (4) test performed as a release test on the (b) (4);
- (b) (4) used as critical reagents for the virus concentration and identification tests performed on CYD virus (b) (4) and lyophilized vaccine antigen and for the test for extraneous agents using (b) (4) performed on the (b) (4).

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. CBER reviewed these CPs and agreed with the reporting category of annual report for the changes specified in the CPs listed above.

b) CBER Lot Release

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

c) Facilities review/inspection

Facilities information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of DENGVAXIA are listed in Table 6. In addition, the activities performed and inspectional histories are noted in Table 6 and are further described in the paragraph that follows.

Table 6: Manufacturing Facilities Table for DENGVAXIA

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Results/ Justification
Manufacture of the Drug Substance (DS), Quality Control testing of DS & DP including release testing **Sanofi Pasteur Inc. ((b) (4))** (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER/Team Biologics (b) (4) VAI
Manufacture of the Drug Product (DP) and Quality Control testing of DP including release testing **Sanofi Pasteur SA ((b) (4))** (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER/Team Biologics (b) (4) VAI
Quality Control Testing (Vaccine) **Sanofi Pasteur SA ((b) (4))** (b) (4)	(b) (4)	(b) (4)	Waived	Team Biologics (b) (4) VAI
Final Bulk Product manufacturing (Diluent), Labeling and Packaging (Vaccine and Diluent), Quality Control (Vaccine and Diluent) and Stability Testing (Diluent)	2518760	086723285	Waived	CBER 10/22-26/2018 VAI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Results/ Justification
Sanofi Pasteur, Inc. (SWR) Discovery Drive Swiftwater, PA 18370-0187				
In vivo Quality Control testing of Diluent for release **Sanofi Pasteur Ltd.** 1755 Steeles Avenue West Toronto, Ontario M2R 3T4 Canada	3002888623	208206623	Waived	Team Biologics 9/6-22/2017 VAI

VAI: Voluntary Action Indicated

CBER conducted a pre-license inspection (PLI) of Sanofi's (b) (4) facility (FEI (b) (4)), (b) (4) for DS manufacturing and QC lab release testing activities related to DENGVAXIA manufacturing. At the end of the inspection, CBER issued a Form FDA 483. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as Voluntary Action Indicated (VAI). All inspectional issues were resolved.

CBER conducted a PLI of Sanofi's (b) (4) , France facility (FEI: (b) (4)), (b) (4) for DP manufacturing and QC lab release testing activities related to DENGVAXIA manufacturing. At the end of the inspection, CBER issued a Form FDA 483. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. The inspection was classified as VAI. All inspectional issues were resolved.

Team Biologics conducted a surveillance inspection of the Sanofi Pasteur (b) (4) facility (FEI (b) (4)), (b) (4) . The inspection was classified as VAI. All inspectional issues were resolved.

CBER conducted a pre-approval inspection of the Sanofi Pasteur Inc. (SWR), PA, USA facility (FEI 2518760), October 22-26, 2018. The inspection was classified as VAI. All inspectional issues were resolved.

Team Biologics performed a surveillance inspection of the Sanofi Pasteur Ltd. Toronto, Canada facility (FEI 3002888623), September 6-22, 2017. The inspection was classified as VAI. All inspectional issues were resolved.

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as

the manufacturing of this product will not increase the use of the active moiety and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

For the nonclinical safety evaluation, CYD vaccine (vaccine manufactured by the same process as DENGVAXIA but with a dose of CYD virus ranging from 5.0 $\log_{10}$ $CCID_{50}$ to 8.0 $\log_{10}$ $CCID_{50}$) was evaluated in a general repeat dose toxicity study in monkeys. Developmental and reproductive toxicity (DART) studies included two immunogenicity/viremia studies in mice and rabbits, two investigational and two pivotal reproductive developmental toxicity studies in mice and rabbits, and a lactation study in mice.

CYD vaccine was evaluated in a repeat-dose toxicity study in monkeys in which systemic toxicity and local tolerance were assessed after three full human dose subcutaneous (SC) administrations. The vaccine was well tolerated, and no vaccine related systemic or local toxicity was identified.

The rabbit and the mouse models were confirmed as acceptable for DART studies by robust antibody response in rabbits and detectable viremia in mice after intravenous administration. The rabbit model was therefore selected for the evaluation of the effects of the antibody response, but not viremia. The mouse model was selected for the evaluation of viremia and its effects, but not antibody response. In rabbits, no indication of maternal systemic toxicity, no test article-effects on mating performance and fertility, no indication of teratogenic potential of the test vaccine, and no effect on pre and post-natal development of the pups were observed when a full human dose (5 $\log_{10}$ $CCID_{50}$) was administered twice before mating and three times during gestation. In the mouse model, animals were administered one IV injection at doses of 5 (one full human dose), 6.5 or 8 $\log_{10}$ $CCID_{50}$ on Day of Gestation (DG) 6, 9 or 12. The doses of 6.5 and 8 $\log_{10}$ $CCID_{50}$ induced reductions in maternal body weight gains and food consumption and increases in post-implantation loss. The most pronounced effects occurred in females given 8 $\log_{10}$ $CCID_{50}$ on DG 9 and were associated with reduced fetal body weights in litters of females given 8 $\log_{10}$ $CCID_{50}$ on DG 9 or 12. Changes at the fetal examination were limited to delays in skeletal ossification at 6.5 or 8 $\log_{10}$ $CCID_{50}$ of CYD vaccine, where reductions in the fetal body weights and maternal toxicity occurred, but no fetal abnormalities. At 5 $\log_{10}$ $CCID_{50}$ CYD vaccine, there were no changes of toxicological significance.

One intravenous injection of CYD vaccine at 5, 6.5 and 8 $\log_{10}$ $CCID_{50}$ in lactating mice on lactation day 14 was generally tolerated with treatment-related effects limited to a transient body weight loss on the day after injection in females given 6.5 and 8 $\log_{10}$ $CCID_{50}$ and no treatment-related changes in litter parameters at any dose.

In addition, the safety of DENGVAXIA was evaluated in distribution, persistence and shedding studies, as well as studies evaluating the viscerotropism, neurotropism and

neurovirulence of the vaccine. No findings of concern regarding vaccine safety were identified in these studies.

5. CLINICAL PHARMACOLOGY

Pharmacodynamic data, comprised of humoral immune responses to DENGVAXIA, were obtained in the clinical studies. The data demonstrated that DENGVAXIA induces a dengue serotype-specific humoral immune response against the Envelope protein. The exact immunologic mechanism that confers protection against dengue is unknown.

6. CLINICAL/STATISTICAL

a) Clinical Program

Overview

The applicant included data from 17 clinical studies in the BLA. The pivotal clinical studies which will be discussed in this SBRA are shown in Table 7.

Table 7. Overview of Pivotal Clinical Studies

Study ID	**CYD15**	**CYD14**	**CYD23**	**CYD57**	**CYD17**
NCT ID	01374516	01373281	00842530	01983553	01134263
Phase	3	3	2	2	3
Countries	Brazil, Colombia, Honduras, Mexico, Puerto Rico	Indonesia, Malaysia, Thailand, Philippines, Vietnam	Thailand	Thailand	Australia
Enrollment	20,869	10,275	4,002	3,203	715
Age	9 - 16 YOA	2 - 14 YOA	4 - 11 YOA	4 - 11 YOA	18-60 YOA
Purpose	Evaluate VE for prevention of dengue (pivotal clinical endpoint study)	Evaluate VE for prevention of dengue (pivotal clinical endpoint study)	Evaluate VE for prevention of dengue (pivotal clinical endpoint study)	Follow-up extension study for CYD 23	Demonstrate lot-to-lot consistency
Control	Saline Placebo	Saline Placebo	Saline Placebo	Saline Placebo	Saline Placebo
Groups	2 groups, randomized 2:1 to receive DENGVAXIA or Placebo SC	2 groups, randomized 2:1 to receive DENGVAXIA or Placebo SC	2 groups, randomized 2:1 to receive DENGVAXIA or Placebo SC	2 groups, randomized 2:1 to receive DENGVAXIA or Placebo SC	5 groups, randomized 3:3:3:3:1 to receive DENGVAXIA or Placebo SC
Schedule	M0, M6, M12	M0, M6, M12	M0, M6, M12	N/A	M0, M6, M12
Total follow-up	6 years	6 years	2 years	4 years	18 months

YOA: Years of age; **VE**: Vaccine efficacy; **SC**: Subcutaneous; **M**: Month; **N/A:** not applicable

Studies **CYD15**, **CYD14**, and **CYD23** had similar designs. CYD15 enrolled 20,869 subjects 9 through 16 years of age (YOA) living in Brazil, Colombia, Honduras, Mexico, and Puerto Rico. CYD14 enrolled 10,275 subjects 2 through 14 YOA living in Indonesia, Malaysia, Thailand, Philippines, and Vietnam. CYD23 enrolled 4,002 subjects 4 through 11 YOA living in Thailand. Each study randomized subjects 2:1 to receive DENGVAXIA vaccine or saline placebo (0.9% sodium chloride) control. The primary objective for each study was to assess the efficacy of DENGVAXIA after three vaccinations at 0, 6 and 12 months in preventing symptomatic virologically-confirmed dengue (VCD) cases, regardless of the severity, due to any of the four serotypes in study subjects. For CYD15 and CYD14 (Phase 3 studies), the primary study objective success criterion was met if the lower bound of the 95% CI around the point estimate of vaccine efficacy (VE) was above 25%. For CYD23 (Phase 2 study), the primary study objective success criterion was met if the lower bound of the 95% CI around the point estimate of VE was above 0%. Each study had the same primary efficacy endpoint case definition consisting of the clinical sign of fever and virologic confirmation of dengue by RT-PCR and/or dengue non-structural protein 1 (NS1) ELISA Antigen Test; Fever was defined in the Phase 3 studies, CYD15 and CYD14, as two consecutive days with temperature ≥ 38°C and in the Phase 2 study, CYD23, as one day with temperature ≥ 37.5°C. Cases were counted during the Active Phase of the studies (through 13 months post-injection 3).

Secondary objectives in each study were: to describe the occurrence of severe adverse events (SAEs), including serious adverse events of special interest (AESIs), in all subjects throughout the trial period, from the date of first injection through the end of year 5; to describe the occurrence of hospitalized virologically-confirmed dengue cases and the occurrence of severe, virologically-confirmed dengue cases, through the end of year 5 (data submitted in the BLA); to describe the reactogenicity of DENGVAXIA vaccine after each dose in a subset of participants; to describe the antibody response to each dengue serotype after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3 in a subset of participants; and to describe the efficacy of DENGVAXIA in preventing symptomatic, virologically-confirmed dengue cases by serotype.

CYD15 results: As shown in Table 8, at the end of study analysis, there were 176 cases of VCD recorded in the per-protocol analysis set for efficacy (PPSE) of the DENGVAXIA group (N = 11,792) and 221 cases in the PPSE of the Placebo group (N = 5,809). The overall VE against VCD in subjects 9 through 16 YOA was 60.8% (95% CI: 52.0 to 68.0). Therefore, the primary study objective of VE against VCD in subjects 9 through 16 YOA was met as the lower bound of the 95% CI of the point estimate of VE was above 25%.

Table 8. Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue Post-Dose 3 During Active Phase Due to Any of the 4 Serotypes for Study CYD15 (PPSE[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
DENGVAXIA N[4] = 12,574	176	176	11,792	1.5 (1.3, 1.7)	**60.8 (52.0, 68.0)**
Placebo N = 6,271	221	221	5,809	3.8 (3.3, 4.3)	--

Source: Adapted from STN 125862/0 Clinical Study Report for CYD15 table 5.1
[1]**PPSE** = Per-protocol analysis set for efficacy
[2]**Cases**: number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-injection 3 through 13 months post-injection 3
[3]**VE** = Vaccine efficacy, success criterion was met if the LB of the of the 95%CI for VE was > 25%
[4]**N** = Number in treatment group, PPSE

Efficacy Analyses by Baseline Dengue Serostatus

Analyses on the efficacy of DENGVAXIA to prevent VCD in subjects 9 through 16 YOA by baseline serostatus was conducted by comparing VE of subjects who tested positive for a previous dengue infection (reciprocal $PRNT_{50}$ titer ≥ 10 for one or more dengue serotypes) at baseline versus subjects who tested negative for a previous dengue infection (reciprocal $PRNT_{50}$ titer < 10 for all four dengue serotypes). Only subjects in the full analysis set for immunogenicity (N = 1992) had blood collected at baseline in CYD15.

As presented in Table 9, the VE against VCD in subjects 9 through 16 YOA with dengue positive serostatus at baseline was 83.7% (95% CI: 62.2 to 93.7). The VE against VCD in subjects 9 through 16 YOA with negative dengue serostatus at baseline was 43.2% (95% CI: -61.6 to 80.0). There were no predefined success criteria for VE against VCD when stratified by dengue serostatus at baseline. However, the lower bound of the 95% CI around the point estimate of VE was above 25% for the subgroup with positive dengue serostatus at baseline, but not for the subgroup with negative dengue serostatus at baseline.

Table 9. Vaccine Efficacy Against Virologically-Confirmed Dengue Cases During the Active Phase by Baseline Dengue Serostatus for Study CYD15 (FASI[1])

Treatment group and Baseline Dengue Serostatus[2]	Cases[3]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[4] (95% CI)
DENGVAXIA Group Baseline Positive Serostatus N[5] = 1,073	8	8	2,116	0.4 (0.2, 0.7)	83.7 (62.2, 93.7)
Placebo Group Baseline Positive Serostatus N = 512	23	23	994	2.3 (1.5, 3.5)	--
DENGVAXIA Group Baseline Negative Serostatus N = 258	9	9	500	1.8 (0.8, 3.4)	43.2 (-61.6, 80.0)
Placebo Group Baseline Negative Serostatus N = 149	9	9	284	3.2 (1.5, 5.9)	--

Source: Adapted from STN 125862/0 Integrated Summary of Efficacy for CYD15 Table 3.6.5.15

[1]**FASI:** Full analysis set for immunogenicity

[2]Serostatus as determined by $PRNT_{50}$ assay; positive defined as reciprocal $PRNT_{50}$ titer ≥ 10 for one or more dengue serotypes; negative defined as reciprocal $PRNT_{50}$ titer < 10 for all four dengue serotypes

[3]**Cases**: number of subjects with at least one symptomatic virologically-confirmed dengue episode post-injection 1 through 13 months post-injection 3

[4]**VE:** Vaccine efficacy, descriptive secondary endpoint

[5]**N:** Number in immunogenicity subset

CYD14 results: As shown in Table 10, at the end of study analysis, there were 117 cases of VCD recorded in the PPSE of the DENGVAXIA group (N = 6,709) and 133 cases in the PPSE of the Placebo group (N = 3,350). The overall VE against VCD in subjects 2 through 14 YOA was 56.5% (95% CI: 43.8 to 66.4). Therefore, the success criterion for the primary study objective of VE against VCD in subjects 2 through 14 YOA was met, as the lower bound of the 95% CI of the point estimate of VE was above 25%. The VE against VCD in the subgroup of study subjects 9 through 14 YOA was 69.6% (95% CI: 43.8 to 66.4). There were no predefined success criteria for VE against VCD for the subgroup of subjects 9 through 14 YOA. However, the lower bound of the 95% CI of the point estimate of VE was above 25%.

Table 10. Vaccine efficacy against symptomatic virologically-confirmed dengue post-dose 3 due to any of the 4 serotypes in subjects ages 2–14 years (PPSE[1]) and 9–14 years (FASE[2]) for study CYD14

Treatment group	Cases[3]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[4] (95% CI)
DENGVAXIA (PPSE) Ages 2 -14 years N[5] = 6,709	117	117	6,525	1.8 (1.5, 2.1)	**56.5** **(43.8, 66.4)**
Placebo (PPSE) Ages 2 -14 years N = 3,350	133	134	3,227	4.1 (3.5, 4.9)	--
DENGVAXIA (FASE) Ages 9 -14 years N = 3,286	13	13	3,187	0.4 (0.2, 0.7)	**69.6** **(36.3, 86.0)**
Placebo (FASE) Ages 9 -14 years N = 1,466	21	21	1,566	1.3 (0.8, 2.0)	--

Source: Adapted from STN 125862/0 Clinical Study Report for CYD14 table 5.1
[1]**PPSE:** Per protocol analysis set for efficacy
[2]**FASE:** Full analysis set for efficacy, cases were counted after the first dose of study vaccine
[3]**Cases:** number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-injection 3 through 13 months post-injection 3
[4]**VE:** Vaccine efficacy, success criterion was met if the LB of the of the 95%CI for VE was > 25% for the 2 -14 years age group
[5]**N:** Number in treatment group, PPSE

Efficacy Analyses by Baseline Dengue Serostatus

Analyses on the efficacy of DENGVAXIA to prevent VCD in subjects 9 through 14 YOA by baseline serostatus were conducted by comparing VE of subjects who tested positive for a previous dengue infection (reciprocal $PRNT_{50}$ titer ≥ 10 for one or more dengue serotypes) at baseline versus subjects who tested negative for a previous dengue infection (reciprocal $PRNT_{50}$ titer < 10 for all four dengue serotypes). Only subjects in the full analysis set for immunogenicity (N = 926) had blood collected at baseline in CYD14.

As presented in Table 11, the VE against VCD in subjects 9 through 14 YOA with positive serostatus at baseline was 79.2% (95% CI: 47.2 to 92.7). The VE against VCD in subjects 9 through 14 YOA with negative serostatus at baseline was 61.6% (95% CI: -21.1 to 88.1). There were no predefined success criteria for VE against VCD when stratified by dengue serostatus at baseline. However, the lower bound of the 95% CI around the point estimate of VE was above 25% for the subgroup with positive dengue serostatus at baseline, but not for the subgroup with negative dengue serostatus at baseline.

Table 11. Vaccine Efficacy Against Virologically-Confirmed Dengue Cases During the Active Phase by Baseline Flavivirus Status in Subjects Ages 9–14 Years for Study CYD14 (FASE[1])

Treatment group and Baseline Dengue Serostatus[2]	Cases[3]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[4] (95% CI)
DENGVAXIA Group Baseline Positive Serostatus N[5] = 487	7	7	981	0.7 (0.3, 1.5)	79.2 (47.2, 92.7)
Placebo Group Baseline Positive Serostatus N = 251	17	18	496	3.4 (2.0, 5.4)	--
DENGVAXIA Group Baseline Negative Serostatus N = 129	7	8	256	2.7 (1.1, 5.6)	61.6 (-21.1, 88.1)
Placebo Group Baseline Negative Serostatus N = 59	8	8	112	7.1 (3.1, 13.6)	--

Source: Adapted from STN 125862/0 Integrated Summary of Efficacy for CYD14 Table 3.6.5.15
[1]FASI: Full analysis set for immunogenicity
[2]Serostatus as determined by $PRNT_{50}$ assay; positive defined as reciprocal $PRNT_{50}$ titer ≥ 10 for one or more dengue serotypes; negative defined as reciprocal $PRNT_{50}$ titer < 10 for all four dengue serotypes
[3]**Cases:** number of subjects with at least one symptomatic virologically-confirmed dengue episode post-injection 1 through 13 months post-injection 3
[4]**VE:** Vaccine efficacy, descriptive secondary endpoint
[5]**N:** Number in immunogenicity subset

CYD23 results: As shown in Table 12, at the end of study analysis, there were 45 cases of VCD recorded in the PPSE of the DENGVAXIA group (N = 2,452) and 32 cases in the PPSE of the Placebo group (N = 1,221). The overall VE against VCD in subjects 4 through 11 YOA was 30.2% (95% CI: -13.4 to 56.6). Therefore, the success criterion for the primary study objective of VE against VCD in subjects 4 through 11 YOA was not met as the lower bound of the 95% CI around the point estimate of VE was below 0%.
As shown in Table 12, the VE against VCD in subjects 9 through 11 YOA was 70.1% (95% CI: 9.3 to 91.1). There were no predefined success criteria for VE against VCD for the subgroup of subjects 9 through 11 YOA. However, the lower bound of the 95% CI around the point estimate of VE was above 0%.

Table 12. Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue Post-Dose 3 Due to Any of the 4 Serotypes for Study CYD23 (PPSE[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
DENGVAXIA Ages 4-11 years N[4] = 2,452	45	45	2,522	1.8 (1.3, 2.4)	**30.2 (-13.4, 56.6)**
Placebo Ages 4–11 years N = 1,221	32	33	1,251	2.6 (1.8, 3.6)	--
DENGVAXIA Ages 9-11 years N = 1,011	6	6	1,033	0.6 (0.2, 1.3)	**70.1 (9.3, 91.1)**
Placebo Ages 9-11 years N = 502	10	10	514	1.9 (0.9, 3.5)	--

Source: Adapted from STN 125862/0 Clinical Study Report for CYD23 table 5.1, and Integrated Summary of Efficacy table 3.6.5.2

[1]**PPSE:** Per-protocol analysis set for efficacy

[2]**Cases:** number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-injection 3 through 13 months post-injection 3

[3]**VE:** Vaccine efficacy, success criterion was met if the LB of the of the 95%CI for VE was > 0% for the 4 – 11 years age group

[4]**N:** Number in treatment group, PPSE

Efficacy Analyses by Baseline Dengue Serostatus

As with studies CYD15 and CYD14, VE based on pre-vaccination dengue serostatus was assessed, but there were too few cases for which this information was known to draw meaningful conclusions.

Lot Consistency

CYD17 was a phase 3, randomized, observer-blind, multicenter, placebo-controlled study to evaluate lot-to-lot consistency, immunogenicity, safety and reactogenicity of four lots of DENGVAXIA when administered SC to adults 18 to 60 years of age. The study enrolled 715 subjects randomized 3:3:3:3:1 to receive three doses from one of four lots of DENGVAXIA (three Phase 3 lots and one Phase 2 lot) or placebo. The success criterion for the primary objective of lot-to-lot consistency was met, as the two-sided 95% CIs of the geometric mean titer ratios for each of the four dengue serotypes were contained within the pre-specified interval of [0.5 and 2] for each of the three pairwise lot-to-lot comparisons. No safety signals were identified in the final study report included in the BLA.

Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were conducted at five clinical investigator study sites that participated in the conduct of Study CYD14 (two sites) and Study CYD15

(three sites). The inspections did not reveal significant problems that impact the data submitted in support of this BLA.

b) Pediatrics

A presentation of Sanofi Pasteur's Pediatric Plan was made to the FDA Pediatric Review Committee (PeRC) on April 10, 2019. The committee agreed with the applicant's request for a waiver of studies of DENGVAXIA in subjects 0 to less than 6 months of age because studies are impossible or highly impractical. Clinical endpoint studies in this pediatric age subgroup are impossible or highly impractical to conduct because the estimated annual number of dengue cases in infants 0 to less than 6 months of age with laboratory-confirmed prior dengue infection and living in endemic areas is low and widely dispersed. The committee agreed with the applicant's request for a deferral of studies in subjects 6 six months to < 2 years of age because pediatric studies should be delayed until additional safety or effectiveness data have been collected (Section 505B(a)(3)(ii) of the Pediatric Research Equity Act (PREA)). The committee agreed with the applicant's request for a deferral for studies in subjects 2 to < 9 years of age because the biological product is ready for approval for use in individuals 9 through 16 years of age before pediatric studies in subjects 2 to < 9 years of age are completed (Section 505B(a)(3)(A)(i) of PREA).

The PREA required studies specified in the approval letter and agreed upon with Sanofi Pasteur are as follows:

1. Study CYD14 under PREA to evaluate the safety and effectiveness of DENGVAXIA in children 2 to < 9 years of age.

2. Study CYD23 under PREA to evaluate the safety and effectiveness of DENGVAXIA in children 4 to < 9 years of age.

3. Study CYD57 under PREA to evaluate the safety and effectiveness of DENGVAXIA in children 4 to < 9 years of age.

4. Study CPIF133 under PREA to evaluate safety and effectiveness of DENGVAXIA in infants and children 6 months to < 2 years of age.

7. SAFETY/ PHARMACOVIGILANCE

Solicited local and systemic adverse reactions (reactogenicity) are indicated below from study CYD15. Reactogenicity for all of the studies submitted to the BLA was similar to CYD15. For CYD15, there were 2,000 subjects 9 through 16 years of age in the safety database for reactogenicity. The most common solicited local and systemic adverse reactions in DENGVAXIA vaccine recipients were headache (39.9%), injection site pain (32.4%), myalgia (29.2%), asthenia (24.6%), malaise (24.5%), and fever (6.8%) were.

There were 11 deaths in the DENGVAXIA group and 11 deaths in the Placebo group in the Active Phase for studies CYD15, CYD14 and CYD23. There were no deaths attributable to vaccination in any subject in any study. The percentage of any SAEs that were not severe dengue was similar between DENGVAXIA and placebo control groups in each study.

There were three cases of serious but non-fatal adverse events attributable to DENGVAXIA vaccination in the pooled analysis of safety data from CYD14 + CYD15: asthma attack (day of Dose 1), urticaria (day of Dose 2) and convulsion (day of Dose 1). All subjects recovered completely. Because the CYD virus components of DENGVAXIA include a yellow fever vaccine virus backbone, potential cases of viscerotropic and neurotropic disease were monitored during the studies, and no cases of either were reported in any of the three clinical efficacy endpoint studies.

Severe Dengue Disease

Cases of severe/hospitalized dengue were considered to be a SAE. During follow-up, in analyses stratified by age, a safety signal for increased risk of hospitalized VCD in younger subjects (particularly 2 to 5 years of age) became apparent. Dengue exposure tracks with age, so these findings raised the possibility that absence of pre-existing dengue immunity predisposed vaccinated subjects to severe disease. Because pre-vaccination blood was drawn on only a subset (~2,000 subjects; the "immunogenicity subset") of the overall efficacy study population, pre-vaccination serostatus was not available for the majority of subjects who became hospitalized VCD cases during the Hospital Phase. Therefore, no definitive conclusions could be reached about the signal of risk in the baseline seronegative population.

To further investigate and characterize this safety signal, the applicant used an ELISA assay against the dengue virus protein NS1. In contrast to the dengue neutralization assay ($PRNT_{50}$), the NS1 assay can distinguish the immune response to vaccination from the immune response to natural dengue exposure. It was possible to optimize this feature of the assay because of the difference between NS1 in the yellow fever virus backbone of the vaccine compared with NS1 expressed by wild type dengue virus. By running the NS1 assay on stored sera that had been collected from subjects post-dose 3, the sponsor was able to determine with reasonable accuracy whether the subjects who became hospitalized VCD cases were dengue immune or non-immune at the beginning of the study. The resulting data were used to impute baseline serostatus for a series of exploratory analyses to assess the risk of hospitalized VCD.

As shown in Table 13, in subjects who had not had a previous dengue infection at baseline, there were more severe dengue cases in subjects who received DENGVAXIA compared to placebo control subjects, yielding an increased Hazard Ratio (HR) for severe/hospitalized dengue for DENGVAXIA vaccinated subjects, dengue non-immune at baseline of: (HR, 9-16 years; CYD14 + CYD15 + CYD23 + CYD57) 6.25 (95% CI: 0.81; 48.32). In contrast, for subjects dengue immune at baseline, the HR for severe/hospitalized dengue was favorable compared to placebo control subjects: (HR, 9-16 years; CYD14 + CYD15 + CYD23 + CYD57) 0.18 (95% CI: 0.09;0.37).

Table 13: Number of Events and Incidence of Severe Dengue* From Month 13 to approximately Month 66 in Children 9 through 16 Years of Age, by Previous Dengue Infection Status, in Studies CYD14, CYD15, CYD23, and CYD57

Dengue Infection Status at Month 13†	DENGVAXIA n (Incidence‡, %)	Placebo n (Incidence‡, %)	Hazard Ratio of Severe Dengue (95% CI)
Previous Dengue Infection	10 (0.068)	27 (0.401)	0.18 (0.09; 0.37)
No Previous Dengue Infection	12 (0.380)	1 (0.069)	6.25 (0.81; 48.32)

n: number of subject with severe dengue cases
CI: confidence interval

* Severe Dengue according to IDMC (Independent Data Monitoring Committee) definition: Proven dengue fever (2 days fever + virological confirmation) plus one of the following: (a) Platelet count ≤ 100,000/µL and bleeding plus plasma leakage (effusion on chest x-ray [CXR] or clinically apparent ascites including imaging procedures or hematocrit ≥ 20% above baseline recovery level or standard for age if only one reading); (b) shock; (c) bleeding (requiring blood transfusion); (d) encephalopathy; (e) liver impairment; (f) impaired kidney function; (g) myocarditis, pericarditis or clinical heart failure.

† Based on measured Dengue anti-NS1 IgG ELISA at Month 13 from first vaccination (Immune= ≥ 9EU/mL).

‡ Cumulative incidence over 4 years from 13 months after the first vaccination.

These safety findings of increased relative risk for severe/hospitalized dengue in subjects who were not previously infected with dengue prior to vaccination led to limitation of the vaccine indication to individuals with laboratory confirmation of a previous dengue infection. Previous dengue infection can be assessed through a medical record documenting a laboratory-confirmed dengue infection or through serological testing prior to vaccination. At this time, no serological test is cleared by FDA for determination of previous dengue infection. Because the positive predictive value of any serological test depends on the local incidence of dengue and potential for false positive results (e.g., due to cross-reactivity with other flaviviruses), the indication proposed by the Sanofi Pasteur was further restricted to individuals living in dengue endemic areas.

Pharmacovigilance Plan (PVP)

Sanofi has proposed a Pharmacovigilance Plan (PVP) for DENGVAXIA with a safety specification to address Identified Risks, Important Potential Risks and Missing Information. Studies listed in the PVP are summarized in Table 14 below.

Table 14: Studies listed in the Pharmacovigilance Plan for DENGVAXIA

Study Title Location & Type	Objectives	Safety concerns addressed	Status and final report submission date
DNG11 (Mexico, Brazil and Malaysia): Incidence study	To assess the background incidence of Neurotropic and Viscerotropic-Like Diseases before DENGVAXIA introduction.	YEL-AVD and YEL-AND	Complete 6 Dec 2017
DNG15 (Brazil, Mexico, Philippines, Malaysia): Cohort Event Monitoring study	To evaluate the safety profile of DENGVAXIA in the real-world immunization setting. To describe demographic and comorbid conditions in the population vaccinated with DENGVAXIA.	Safety Exposures in pregnancy, Allergy or anaphylaxis, Viscerotropic and neurotropic diseases	Ongoing 31 Dec 2025
Prospective pregnancy registry (United States)	To collect maternal, fetal, and infant outcomes of potential exposure to dengue vaccine during pregnancy.	Exposure during pregnancy	Planned 31 Dec 2026
(b) (4)	(b) (4)	(b) (4)	(b) (4)
CYD63 (Singapore), CYD64 (Brazil, Colombia, Honduras, Mexico, Puerto Rico), & CYD65 (Colombia, Philippines): Booster studies	To evaluate the safety and immunogenicity of a booster dose administered 4-5 years after the third dose (CYD63 and CYD64). To evaluate the safety and immunogenicity of 1-, 2-, or 3-Dose Schedules Followed by a Single Booster (CYD65).	Waning of protection over time Need for booster	Ongoing 31 Dec 2019 for CYD63 and CYD64 31 Mar 2021 for CYD65
CYD50 (Brazil): Exposure in HIV+ adults	To evaluate immunogenicity and safety in clinically stable HIV+ adults on antiretroviral therapy.	Exposure in immunocompromised population	Planned 30 Jun 2022
CYD66 (Philippines), CYD67 (Malaysia), and CYD71 (Mexico): Co-administration studies	The studies evaluate the safety and immunogenicity of co-administration of CYD dengue vaccine with other vaccines: booster dose of Tdap (CYD66), HPV Vaccine (CYD67 and CYD71).	Co-administration with Tdap, HPV vaccines	Ongoing 31 Dec 2020

YEL-AND: Yellow Fever (Vaccine)-Associated Neurotropic Disease, **YEL-AVD:** Yellow Fever (Vaccine)-Associated Viscerotropic Disease

Studies CYD14, CYD15, and CYD57 are also included in the PVP. These studies are described in detail above. The proposed pharmacovigilance plan for DENGVAXIA (Risk

Management Plan, version 5.0, dated August 1, 2018) is adequate for the labeled indication. No additional Post-Marketing Commitments or Post-Marketing Requirements are necessary.

8. ADVISORY COMMITTEE MEETING

A Vaccines and Related Biological Products Committee (VRBPAC) meeting was convened on March 7, 2019. The committee discussed the safety and efficacy data derived from the clinical disease endpoint efficacy studies conducted in subjects 2 - 16 years of age in the Asian Pacific Region and South America, including Puerto Rico. As part of the discussion, the committee was asked to focus on the age group of 9 - 16 years. In its deliberations, the committee considered the epidemiology of dengue disease in Puerto Rico. The committee noted that data support the efficacy of DENGVAXIA in pediatric subjects with confirmed prior dengue infection and living in endemic areas. The committee expressed concern about the safety signal identified in the efficacy studies, namely an increased risk of hospitalization and severe dengue in individuals with no prior exposure to dengue who were vaccinated with DENGVAXIA and subsequently infected with dengue. There was consensus that the dengue infection status of individuals would need to be determined prior to vaccination if the vaccine was licensed and recommended for use. The committee expressed concern that currently available serological tests may lead to false positive results because of cross-reactivity with other flaviviruses. The committee also noted the operational/logistical and infrastructure concerns of serotesting prior to vaccination. There was broad recognition of the value of an FDA cleared rapid diagnostic assay to establish prior exposure to dengue in individuals to be vaccinated.

The committee expressed concern about inferring vaccine effectiveness in adults 18 to 45 years of age based on the pediatric efficacy studies and antibody titers in adults because available immunogenicity data in adults were derived from small studies and conducted in countries with high dengue endemicity, i.e., Vietnam and India. The committee was concerned that these data may not reflect immune responses in adults living in Puerto Rico. The committee opined that in the absence of immunogenicity data more relevant to adults living in Puerto Rico, it was difficult to infer effectiveness in the adult population.

The VRPBAC voted on four questions.

1. Are the available data adequate to support the effectiveness of DENGVAXIA for the prevention of dengue disease caused by dengue virus serotypes 1,2, 3 and 4 in persons 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   The results of the vote were as follows:

   Yes = 6 No = 7 Abstain = 1

2. Are the available data adequate to support the safety of DENGVAXIA when administered to persons 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   The results of the vote were as follows:

   Yes = 7 No = 7 Abstain = 0

3. Are the available data adequate to support the effectiveness of DENGVAXIA for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in persons 9 through < 17 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   The results of the vote were as follows:

   Yes = 13 No = 1 Abstain = 0

4. Are the available data adequate to support the safety of DENGVAXIA when administered to persons 9 through < 17 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   The results of the vote were as follows:

   Yes = 10 No = 4 Abstain = 0

The committee's concerns were discussed between Sanofi Pasteur and CBER after the March 7, 2019, VRPBAC meeting. Both CBER and Sanofi Pasteur agreed that additional studies relevant to the adult population in Puerto Rico would address the committee's concerns and could support inclusion of individuals 17 through 45 years of age in the indication. Sanofi Pasteur informed CBER that they decided for this BLA submission to pursue an indication only for individuals 9 through 16 years of age and requested a revised indication that does not include individuals 17 through 45 years of age.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable.

10. LABELING

The proprietary name, DENGVAXIA, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on September 27, 2018, and found to be acceptable. CBER communicated this decision to Sanofi Pasteur on November 14, 2018. The APLB found the prescribing information (PI) and package/container labels to be acceptable from a promotional and comprehension perspective.

The Review Committee negotiated revisions to the PI, including modifying the proposed proper name from "Dengue Tetravalent Vaccine (Live, Attenuated)" to "Dengue Tetravalent Vaccine, Live."

The indication and limitations of use section of the PI was revised during labeling negotiations. CBER requested that the risk of severe dengue disease associated with

DENGVAXIA in subjects with no previous dengue infection be clearly communicated in the limitations of use section and that it be clearly stated in the PI that DENGVAXIA was not studied in or indicated for persons who live in dengue non-endemic areas and travel to dengue endemic areas.

CBER and Sanofi Pasteur negotiated language in the PI to clearly indicate that DENGVAXIA should only be administered to subjects 9 through 16 year of age and living in dengue endemic areas who have a laboratory-confirmed previous dengue infection. Given the broad recognition of the value of an FDA cleared test to establish a previous dengue infection, a decision was taken to state in the PI that no FDA cleared diagnostic test is currently available for this purpose. When an FDA cleared test becomes available, the PI can be revised to reflect this development.

All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

a) Recommended Regulatory Action

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

b) Risk/Benefit Assessment

Considering the data submitted to support the safety and efficacy of DENGVAXIA that have been presented and discussed in this document, as well as the seriousness of dengue disease, the Review Committee is in agreement that the risk/benefit balance for DENGVAXIA is favorable and supports approval for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

c) Recommendation for Postmarketing Activities

Sanofi Pasteur has committed to conduct the following postmarketing activities, which will be included in the approval letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

1. To establish a pregnancy registry for DENGVAXIA in the United States to prospectively collect data on spontaneously reported exposures to DENGVAXIA at any time during pregnancy. You will submit annual reports as well as a 5-year summary report, after which you will continue enrolling patients in the registry

and submitting annual reports pending CBER review of the reports and determination that the registry can be discontinued.

Final Protocol Submission: 12/31/2019
Study Completion Date: 06/30/2026
Final Report Submission: 12/31/2026

PEDIATRIC REQUIREMENTS

2. Study CYD14 to evaluate the safety and effectiveness of DENGVAXIA in children 2 to < 9 years of age.

   Final Protocol Submission: 01/28/2011
   Study Completion Date: 11/21/2017
   Final Report Submission: 04/01/2020

3. Study CYD23 to evaluate the safety and effectiveness of DENGVAXIA in children 4 to < 9 years of age.

   Final Protocol Submission: 05/27/2011
   Study Completion Date: 09/10/2013
   Final Report Submission: 04/01/2020

4. Study CYD57 to evaluate the safety and effectiveness of DENGVAXIA in children 4 to < 9 years of age.

   Final Protocol Submission: 10/18/2013
   Study Completion Date: 02/19/2016
   Final Report Submission: 04/01/2020

5. Study CPIF 133 to evaluate safety and effectiveness of DENGVAXIA in infants and children 6 months to < 2 years of age.

   Final Protocol Submission: 03/31/2021
   Study Completion Date: 03/31/2027
   Final Report Submission: 03/31/2028

12. REFERENCES

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