Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Deborah Thompson, MD, MSPH Team Leader, Pharmacovigilance Branch 3 (PB3) Division of Pharmacovigilance (DPV), OBPV, CBER Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Sanofi Pasteur Inc.
Product:	Dengvaxia (Dengue Tetravalent Vaccine, Live)
STN:	125682/64
Indication(s):	Prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4. DENGVAXIA is approved for use in individuals 6 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.
Meeting Date:	Pediatric Advisory Committee Meeting, April 29 – 30, 2025

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The triggers for this pediatric postmarketing safety review for DENGVAXIA include:

- May 1, 2019, initial approval of DENGVAXIA Submission Tracking Number (STN) 125682/0 for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas
- June 30, 2023, approval of DENGVAXIA STN 125682/40 to include use in individuals 6 through 8 years of age with laboratory-confirmed previous dengue infection and living in endemic areas

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description and Indication

DENGVAXIA (Dengue Tetravalent Vaccine, Live) is a live attenuated vaccine constructed using recombinant DNA technology by replacing the sequences encoding the pre-membrane (prM) and envelope proteins in the yellow fever (YF) 17D204 vaccine virus genome with those encoding for the homologous sequences of dengue virus serotypes 1, 2, 3, and 4, respectively. It is supplied as a sterile suspension for subcutaneous injection.

DENGVAXIA is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4. DENGVAXIA is approved for use in individuals 6 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

<u>Limitations of use</u>

- DENGVAXIA is not approved for use in individuals younger than 6 years of age. These individuals, regardless of previous infection by dengue virus, are at increased risk of severe and hospitalized dengue disease following vaccination with DENGVAXIA and subsequent infection with any dengue virus serotype.
- 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 nonendemic areas who travel to dengue endemic areas.

1.3 Pertinent Regulatory History

- May 1, 2019: Initial approval of DENGVAXIA STN 125682/0 for use in individuals 9 through 16 years of age
- June 30, 2023: Approval of DENGVAXIA STN 125682/40 to include use in individuals 6 through 8 years of age

The above approvals constitute the regulatory triggers for the current PAC review.

Of note, as per the applicant, DENGVAXIA distribution in the U.S. and globally is planned to be discontinued effective September 2025, with a shelf life up to September 2026 (see additional information in section 6.4 of memorandum).

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
  - VAERS reports for DENGVAXIA during May 1, 2019, to September 30, 2024 (PAC review period)
- Manufacturer's Submissions
  - DENGVAXIA U.S. prescribing information (updated October 2023)
  - Applicant response to information request regarding dose distribution data, received under STN 125682/64
  - Risk Management Plan, Version 7.0 dated February 11, 2022
  - Periodic safety reports
- FDA Documents
  - STN 125682/0 DENGVAXIA approval letter
  - STN 125682/40 DENGVAXIA approval letter
  - STN 125682/40 DENGVAXIA Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety related labeling changes during the PAC review period May 1, 2019, to September 30, 2024.

4 PRODUCT UTILIZATION DATA

The applicant provided estimates of DENGVAXIA distribution data for the U.S. and worldwide for the PAC review period (STN 125682/64): 4,840 doses have been

distributed in the U.S. and 65,428 doses globally. Dengvaxia is approved for administration as a 3-dose regimen, with each dose administered 6 months apart. The sponsor was not able to provide data on proportion of doses distributed to pediatric and adult patients. Note that the number of doses distributed is an estimate of the number of patients vaccinated because doses may have been distributed without being administered to patients or some patients may have received fewer than the recommended 3-doses.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) is the Risk Management Plan, Version 7.0 dated February 11, 2022, and lists the following important identified risks, important potential risks, and missing information for DENGVAXIA (see Table 1).

Table 1: DENGVAXIA Safety Concerns

Important identified risks	• Allergic Reactions (including anaphylactic reactions) • Increased risk of severe and/or hospitalized dengue following vaccination in individuals not previously infected by dengue virus
Important potential risks	• YF vaccine-associated viscerotropic disease (YEL-AVD) • YF vaccine-associated neurotropic disease (YEL-AND)
Missing information	• Safety in immunocompromised subjects (including subjects with congenital or acquired immune deficiency, or with Human Immunodeficiency Virus (HIV) infection with impaired immune function) • Safety profile of inadvertent use in pregnant or lactating women

The important identified risks of allergic reactions, including anaphylactic reactions, and increased risk of severe dengue following vaccination in individuals not previously infected by dengue virus are labeled events in the U.S. prescribing information (USPI). Yellow Fever (YF) vaccine-associated viscerotropic disease (YEL-AVD) and YF vaccine-associated neurotropic disease (YEL-AND) are theoretical risks. The PVP indicates that the risk of viscerotropism and neurotropism has not been substantiated by non-clinical findings and that the risk for these conditions is linked to the E protein of YF virus, which is not present in the recombinant dengue viruses. The PVP also indicates that no cases of YEL-AVD and YEL-AND were identified in premarketing clinical

s tudies.

The important identified and potential risks listed in Table 1 are monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. The PVP also states that for each spontaneous report of suspected viscerotropism or neurotropism that the company receives from Healthcare Professionals or a Health Authority, the company will "proactively propose specific YF laboratory testing (YF 17D virus testing) by a reference laboratory." Please see section 5.2 for discussion of a pregnancy registry as a postmarketing commitment (PMC). There are no postmarketing requirements (PMRs) for safety-related studies or Risk Evaluation and Mitigation Strategy (REMS) for DENGVAXIA.

5.2 Safety-related Postmarketing Studies

The following safety-related postmarketing study was described in STN 125682/0 approval letter dated May 1, 2019.

Postmarketing commitment (PMC)
PMC#5: *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: December 31, 2019
Study Completion Date: June 30, 2026
Final Report Submission: December 31, 2026

Study status: In the Sponsor's periodic safety report (under STN 125682/58) submitted on February 13, 2024, the Sponsor indicated that for the U.S. pregnancy registry study DNG00044, no cases of pregnancy exposure have been reported.

The company also conducted a post-market prospective cohort event monitoring study, Study DNG15, to assess the incidence of selected adverse events. Per the Sponsor's periodic safety report covering December 8, 2022 to December 7, 2023, as of December 22, 2022, a total of 12,593 participants had been enrolled in Study DNG15 with almost all individuals being from the Philippines (81.1%) or Brazil (18.2%); most participants were recruited during public vaccination campaigns offered in 2017 in the Philippines and Brazil. No cases of YEL-AVD or YEL-AND were reported during Study DNG15 and no safety signals were identified. Finally, the PVP includes a study

completed in Latin America and Asia before vaccine launch ("Incidence Study of Viscerotropic-Like and Neurotropic-Like Disease in Dengue-Endemic Regions Multinational, observational, population-based incidence study; Study DNG11) which provided background incidence rates of diseases that can mimic YEL-AVD and YEL-AND.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of DENGVAXIA between May 1, 2019, to September 30, 2024 (PAC review period). VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for DENGVAXIA during the PAC review period are listed in Table 2 below. There were a total of 50 US and 492 foreign reports for the review period May 1, 2019, to September 30, 2024.

Table 2: DENGVAXIA VAERS reports during May 1, 2019, to September 30, 2024

Age	U.S. Serious Non-Fatal*	Foreign Serious Non-Fatal*	U.S. Deaths	Foreign Deaths	U.S. Non-Serious	Foreign Non-Serious	U.S. Total Reported	Foreign Total Reported
<18 years	0	11	0	144	9	0	9	155
≥ 18 years	6	23	0	4	31	0	37	27
Unknown	1	190	0	120**	3	0	4	310
All Ages	7	224	0	268	43	0	50	492

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).
**Note: Based on review of case narratives, one report with a vaccination date after U.S. approval and "unknown age" in Table 2 was determined to involve a pediatric patient. Among the remaining 119 reports listed as "unknown age" 86 were determined to involve pediatric individuals.

6.2.1 Deaths

There were 268 deaths reported during the PAC review period, including 144 pediatric deaths. Of note, all deaths were foreign reports. These reports were individually reviewed and are summarized below. Review of death reports did not identify patterns suggesting new safety concerns for DENGVAXIA.

6.2.2 U.S. Death Reports

There were no death reports in the U.S.

6.2.3 Foreign Death Reports

There were 144 foreign pediatric deaths, all were from the Philippines. Of the 144 foreign pediatric deaths, 143 have a vaccination date prior to U.S. approval (n=54) or did not include information on vaccination date (n=89). The remaining pediatric death report from the Philippines reported three vaccine doses prior to U.S. approval and another vaccine dose after U.S. approval. One additional pediatric death report* with a vaccination date after U.S. approval is described below.

- One report which was from Thailand indicated a vaccination date after U.S. approval. The report age field was blank although the report narrative described a 10-year-old male who experienced high fever and rash throughout the body 2-days post-vaccination; he was diagnosed with Kawasaki's disease with a fatal outcome 6-days post-vaccination.
  (*Was listed initially as "unknown age" but review of the narrative indicated patient age.)

Of the four foreign adult deaths, only one report included a vaccination date, and it was prior to U.S. approval. There were 119 foreign death reports listed as "unknown age". The majority of death reports (n=93) for individuals of "unknown age" did not have vaccination dates reported; 26 death reports indicated vaccination dates prior to U.S. approval. Among the 119 foreign death reports listed as "unknown age", almost all (n=114) were from the Philippines (five were from Brazil). Review of case narratives for the 119 reports listed as ""unknown age", showed 86 of the 119 reports involved pediatric individuals. Death reports for individuals of "unknown age" were often consumer reports from news articles and social media or reports from lawyers, followed by reports from public health authorities and healthcare providers.

Reviewer comment on foreign deaths:

Increased risk of severe dengue following vaccination with Dengvaxia in persons not previously infected

In unvaccinated individuals, first dengue infections rarely cause severe dengue, while second dengue infections with a different serotype are associated with an increased risk of severe dengue. As stated in the USPI, DENGVAXIA administration to individuals not previously infected by dengue virus is associated with an increased risk of severe dengue disease when the vaccinated individual is subsequently infected with any dengue virus serotype. Therefore, healthcare professionals must evaluate individuals for prior dengue infection to avoid vaccinating individuals who have not been previously infected by dengue virus. Previous infection by dengue virus can be evaluated through a medical record of previous laboratory-confirmed dengue infection or through serotesting prior to vaccination.

Philippines experience

A vaccination campaign was underway in the Philippines from 2016 to 2017, years prior to U.S. approval and prior to the identification of the increased risk of severe dengue in seronegative individuals. Use of Dengvaxia in the Philippines was not limited to individuals with laboratory evidence of previous dengue infection. The Philippines revoked the license for Dengvaxia as of February 2019. All of the VAERS death reports for DENGVAXIA were foreign reports, almost all of which indicated vaccination dates prior to U.S. approval or did not provide information on vaccination date. Death reports commonly described individuals who experienced dengue fever following vaccination or who experienced signs and symptoms that could be associated with dengue fever.

Dengvaxia approval in the U.S.

DENGVAXIA was approved in the U.S. on May 1, 2019, for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. The FDA approved indication includes this limitation 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." The USPI also includes Warnings and Precautions for increased risk of severe dengue disease following DENGVAXIA in persons of any age not previously infected with dengue virus.

6.2.4 Serious Reports

During the PAC review period, there were seven serious non-fatal U.S. reports, six of which were in adults, and one was in a patient of unknown age. The most common PTs in these seven reports were COVID-19 (n=3) and unevaluable event (n=2).

Among all serious reports (including deaths), there were 499 serious reports, including 155 pediatric reports and 33 adult reports. (Reports with a fatal outcome were discussed in the previous section.) Age was unknown for the remaining 311 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) in serious reports are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs for serious reports

Preferred Term (PT)	**# Serious Reports**	**Label Status** *USPI update 10/2023 (Label Section)*
Death	259	Labeled, Section 6.2 Postmarketing Experience
Pyrexia	169	Labeled (i.e., fever), Section 6 Adverse Reactions
Dengue fever	130	Labeled, Section 5 Warnings and Precautions, Section 6 Adverse Reactions
Headache	130	Labeled, Section 6 Adverse Reactions
Cerebral hemorrhage	71	Unlabeled
Vomiting	71	Labeled, Section 6 Adverse Reactions
Abdominal pain	61	Labeled, Section 6 Adverse Reactions
Dyspnoea	60	Labeled, Section 6 Adverse Reactions
Autopsy	51	Unlabeled
Anaphylactic Reaction	49	Labeled, Section 5 Warnings and Precautions, Section 6.2 Postmarketing Experience
Internal hemorrhage	44	Unlabeled
Rash	44	Unlabeled
Malaise	41	Labeled, Section 6 Adverse Reactions
Asthenia	40	Labeled, Section 6 Adverse Reactions
Hypersensitivity	37	Labeled, Section 4 Contraindications, Section 5 Warnings and Precautions, Section 6.2 Postmarketing Experience
Illness	36	Unlabeled
Swelling	36	Labeled, Section 6 Adverse Reactions
Pneumonia	34	Unlabeled
Decreased appetite	33	Unlabeled
Diarrhea	32	Unlabeled
Myalgia	32	Labeled, Section 6 Adverse Reactions
Cough	30	Unlabeled

Preferred Term (PT)	# Serious Reports	Label Status *USPI update 10/2023 (Label Section)*
Dizziness	29	Labeled, Section 6 Adverse Reactions
Inflammation	29	Unlabeled
Nausea	28	Unlabeled

Note: The 25 most commonly reported PTs in serious reports for Dengvaxia are shown in above table.

Reviewer comments: More than half (n=14, 56%) of the most frequently reported PTs for serious reports are labeled events. The unlabeled events of cerebral hemorrhage, internal hemorrhage, and autopsy were associated with death reports; severe dengue infection can lead to bleeding, including cerebral or internal hemorrhage. The USPI includes Warnings and Precautions for increased risk of severe dengue disease following DENGVAXIA in persons younger than 6 years of age regardless of previous infection with dengue virus and an increased risk of severe dengue disease following DENGVAXIA in persons of any age not previously infected with dengue virus.

In addition, the unlabeled events of illness, decreased appetite, and inflammation are non-specific and were associated with death reports. The unlabeled event of pneumonia was also mostly associated with death reports. Reports with a fatal outcome were discussed in a previous section.

Furthermore, the unlabeled event of rash was often associated with the labeled events of hypersensitivity and allergic including anaphylactic reactions, as well as viral infections, including dengue fever. The unlabeled event of cough often occurred in individuals experiencing signs and symptoms of common respiratory tract infections, including viral and bacterial infections and pneumonia; some other individuals experienced cough as a symptom of dengue fever or possible hypersensitivity reactions. The unlabeled events of nausea and diarrhea often occurred in individuals experiencing a variety of signs and symptoms that could be consistent with common infectious conditions, including viral or bacterial infections and dengue fever; underlying diagnoses were often not clear. Overall, the most frequent PTs among serious reports were labeled events, related to labeled events, associated with potential alternative etiologies, or were included in reports with limited clinical details to assess the role of the vaccine. Review of the most frequently reported PTs for serious reports did not identify patterns suggesting new safety concerns for DENGVAXIA.

6.2.5 Non-serious Reports

During the reporting period, there were 43 non-serious reports; of which 9 involved pediatric individuals. Table 4 below lists the 10 most frequently reported PTs in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4: Ten most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	Label Status *USPI update 10/2023 (Label Section)*
Expired product administered	7	Not applicable, not an adverse event
Dizziness	4	Labeled, Section 6 Adverse Reactions
Pain in extremity	4	Unlabeled
Chills	3	Unlabeled
Fatigue	3	Unlabeled
Headache	3	Labeled, Section 6 Adverse Reactions
Malaise	3	Labeled, Section 6 Adverse Reactions
No adverse event	3	Not applicable, not an adverse event
Pyrexia	3	Labeled (i.e., fever), Section 6 Adverse Reactions
Chest discomfort	2	Unlabeled
Erythema	2	Labeled

Reviewer comments: The most frequently reported PTs for non-serious reports are labeled events, related or associated with labeled events, or are PTs that do not indicate an adverse event occurred. The unlabeled PT of pain in extremity is related to the labeled events of injection site pain and myalgia. The unlabeled PT of chills can be associated with the labeled event of fever. The unlabeled event of fatigue can be associated with the labeled event of malaise. The unlabeled PT of chest discomfort can be associated with the labeled event of dyspnea. In addition, the most frequently reported unlabeled PTs were each reported in fewer than five individuals. Review of the most frequently reported PTs for non-serious reports did not identify patterns suggesting new safety concerns for DENGVAXIA.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of DENGVAXIA were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run with a data lock date of November 8, 2024, for DENGUE TETRAVALENT (DENGVAXIA) did not identify any PTs with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for DENGVAXIA were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons. Of note, as per the periodic safety report covering 12/8/2022 - 12/7/2023, the applicant notified FDA that DENGVAXIA distribution in the U.S. is planned to be

discontinued effective September 2025 (with a shelf life up to September 2026) due to low demand for this vaccine. The Sponsor indicated that there are limited public health programs in place due to the complexity of the “Screen and Vaccinate” approach that is recommended by the World Health Organization.

7 LITERATURE REVIEW

A search of the U.S. National Library of Medicine’s PubMed.gov database on November 21, 2024, for peer-reviewed literature, with the search term “DENGVAXIA” and “safety” limited by human species, and dates from PAC trigger (May 1, 2019) to date of search (November 21, 2024), retrieved 30 publications. Titles and abstracts were screened for relevance to safety information specifically for DENGVAXIA and its U.S. labeled indication. None of the articles described new postmarketing safety concerns for DENGVAXIA in the U.S. Additional new safety issues were not identified from review of the 30 publications, which included general subject review or commentary (n=14); follow-up on issues and lessons learned related to foreign vaccination campaigns for DENGVAXIA (n=10) including testing assays and/or pre-vaccination screening strategies to identify baseline dengue serostatus, prescriber knowledge of safety messages, effects of vaccination by serostatus, and vaccine hesitancy; experimental trials including alternative DENGVAXIA vaccination schedules, booster doses, or other vaccines (n=4); and basic science/methodology including mosquito larval habitat control (n=2).

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the approval of the May 1, 2019, initial approval of DENGVAXIA STN 125682/0 for use in individuals 9 through 16 years of age and the June 30, 2023, approval of DENGVAXIA STN 125682/40 for use in individuals 6 through 16 years of age. Review of passive surveillance adverse event reports, the sponsor’s periodic safety reports, and the published literature for DENGVAXIA does not indicate any new safety concerns. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of DENGVAXIA.