Our STN: BL 125682/0 **BLA APPROVAL**

Sanofi Pasteur Inc.
Attention: Michael F. Stirr
Discovery Drive
Swiftwater, PA 18370

May 1, 2019

Dear Mr. Stirr:

Please refer to your Biologics License Application (BLA) submitted on August 31, 2018, and received on August 31, 2018, under section 351(a) of the Public Health Service Act (PHS Act) for Dengue Tetravalent Vaccine, Live.

LICENSING

We have approved your BLA for Dengue Tetravalent Vaccine, Live effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Dengue Tetravalent Vaccine, Live under your existing Department of Health and Human Services U.S. License No. 1725. Dengue Tetravalent Vaccine, Live is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. Dengue Tetravalent Vaccine, Live is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

The review of this product was associated with the following National Clinical Trial (NCT) number(s): NCT01064141, NCT00617344, NCT00993447, NCT00875524, NCT00842530, NCT00788151, NCT00880893, NCT01187433, NCT01550289, NCT01488890, NCT01983553, NCT01134263, NCT01436396, NCT01373281, NCT01374516, NCT01411241, NCT01254422, NCT02824198 and NCT02623725.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Dengue Tetravalent Vaccine, Live drug substances at Sanofi Pasteur (b) (4) . The final bulk product will be manufactured at Sanofi Pasteur, (b) (4) filled and lyophilized at Sanofi Pasteur, (b) (4) and labeled and packaged at Sanofi Pasteur Inc., 1 Discovery Drive, Swiftwater, Pennsylvania 18370. The diluent (0.4% NaCl, Saline Diluent) will be manufactured at Sanofi Pasteur Inc., 1 Discovery Drive, Swiftwater, Pennsylvania 18370.

You may label your product with the proprietary name DENGVAXIA. The vaccine will be supplied in a single dose configuration that contains one vial of lyophilized vaccine antigen and one vial of saline diluent.

DATING PERIOD

The dating period for the lyophilized vaccine antigen shall be 36 months from the date of manufacture when stored at 2 °C to 8 °C. The date of manufacture shall be defined as the date of lyophilization of the filled final bulk product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for each of the four monovalent CYD virus drug substances shall be (b) (4) . The dating period for the diluent (0.4% sodium chloride, Saline Diluent) is 24 months from the date of manufacture when stored at 2 °C to 8 °C. The date of manufacture shall be 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.

COMPARABILITY PROTOCOL

This approval also includes comparability protocols for (1) (b) (4) reference standard used in the (b) (4) test performed as a release test on the (b) (4) and (2) (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. In your annual report (21 CFR 601.12(d)), you should report information confirming that the change meet the requirements specified in your approved comparability protocol. Include the information described in 21 CFR 601.12(d)(3).

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Dengue Tetravalent Vaccine, Live, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under Amendment 55, dated May 1, 2019, the draft carton labeling submitted under Amendment 53, dated April 29, 2019, and the draft container labeling submitted under Amendment 49, dated April 24, 2019.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels that are identical to the package and container labels submitted on April 29, 2019, and April 24, 2019, respectively, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA 125682 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-lot-distribution-reports.

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

You have been granted a tropical disease priority review voucher, as provided under section 524 of the FDCA. This voucher entitles you to designate a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This priority review voucher may be transferred by you to another sponsor of a human drug or biologic application. When redeeming this priority review voucher, you should refer to this letter as an official record of the voucher. If the voucher is transferred, the sponsor to whom the voucher has been transferred should include a copy of this letter (which will be posted on our Web site as

are all approval letters) and proof that the voucher was transferred. In addition, this priority review voucher has been assigned a tracking number, PRV BLA 125682. All correspondences related to this voucher should refer to this tracking number. For additional information regarding the priority review voucher, see FDA's guidance, *Tropical Disease Priority Review Vouchers,* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to < 6 months because necessary studies are impossible or highly impracticable. This is because the estimated annual number of dengue cases in infants in this age group with laboratory-confirmed prior dengue infection and living in endemic areas is low and widely dispersed.

We are deferring submission of your pediatric study for ages 6 months to < 2 years for this application because the pediatric studies should be delayed until additional safety or effectiveness data have been collected. We are deferring submission of your pediatric studies for ages 2 years to < 9 years for this application because the drug or biological product is ready for approval for use in individuals 9 through 16 years of age before studies in pediatric subjects ages 2 years to < 9 years are complete.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

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

   Final Protocol Submission: January 28, 2011

   Study Completion Date: November 21, 2017

Final Report Submission: April 1, 2020

2. Deferred study CYD23 to evaluate the safety and effectiveness of DENGVAXIA in children 4 to < 9 years of age.

   Final Protocol Submission: May 27, 2011

   Study Completion Date: September 10, 2013

   Final Report Submission: April 1, 2020

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

   Final Protocol Submission: October 18, 2013

   Study Completion Date: February 19, 2016

   Final Report Submission: April 01, 2020

4. Deferred study CPIF133 to evaluate safety and effectiveness of DENGVAXIA in infants and children 6 months to < 2 years of age.

   Final Protocol Submission: March 31, 2021

   Study Completion Date: March 31, 2027

   Final Report Submission: March 31, 2028

Submit the protocols to your IND 11219, with a cross-reference letter to this BLA 125682 explaining that these protocols were submitted to the IND.

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

We note that you have fulfilled the pediatric study requirement for ages 9 through 16 years for this application.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of April 29, 2019, as outlined below:

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

Please submit clinical protocols to your IND 11219, and a cross-reference letter to this BLA 125682 explaining that this protocol was submitted to the IND.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

(b) (4)

Sincerely,

Marion F. Gruber, Ph.D.
Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research