



Our STN: BL 125682/0

**LATE-CYCLE
MEETING MEMORANDUM**

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

Dear Mr. Stirr:

Attached is a copy of the memorandum summarizing your February 20, 2019, Late-Cycle Meeting (teleconference) with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Stephanie Polo or Ramachandra Naik, PhD, at 301-796-2640.

Sincerely,

Loris McVittie, PhD
Deputy Director - Regulatory
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: February 20, 2019, 9:30 AM – 11:00 AM

Application Number: BLA STN 125682/0

Applicant Name: Sanofi Pasteur, Inc.

Product Name: Dengue Tetravalent Vaccine, Live (DENGIVAXIA)

Proposed Indications: 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. Previous dengue infection can be assessed through a medical record of a previous laboratory confirmed dengue infection or through current serotesting.

Meeting Chair: Kirk Prutzman, PhD

Meeting Recorders: Ramachandra Naik, PhD and Stephanie Polo

FDA ATTENDEES

Nabil Al-Humadi, PhD	OVRP/DVRPA
Meghna Alimchandani	OBE
Marie Anderson, PhD	OCBQ/DBSQC
Steve Anderson, PhD	OBE
Deepa Arya, PhD, MPH, MBA	OBE/DE
Noel Baichoo, PhD	OCBQ/DBSQC
Brenda Baldwin, PhD	OVRP/DVRPA
Lokesh Bhattacharyya, PhD	OCBQ/DBSQC
Qiao Bobo, PhD	OCBQ/DMPQ
Sarah Browne, MD	OVRP/DVRPA
Wambui Chege, PhD	OBE/DE
Mridul Chowdhury, PhD	OBE/DB
Carmen Collazo, PhD	OVRP/DVRPA
Christine Drabick	OCBQ/DIS
Oluchi Elekwachi	OCBQ/DCM
Doran Fink, MD, PhD	OVRP/DVRPA
Cara Fiore, PhD	OVRP/DVRPA
Richard Forshee, PhD	OBE
Sara Gagnetten, PhD	OVRP/DVP
Marion Gruber, PhD	OVRP
Jie He, PhD	OCBQ/DMPQ
Lei Huang, PhD	OBE/DB
Philip Krause, MD	OVRP
Ralph LeBlanc, MD	OVRP/DVRPA
Robin Levis, PhD	OVRP/DVP
Tsai-Lien Lin, PhD	OBE/DB
Loris McVittie, PhD	OVRP/DVRPA

Ramachandra Naik, PhD	OVRP/DVRPA
Malcolm Nasirah	OCBQ/DIS
Stephanie Polo	OVRP/DVRPA
Douglas Pratt, MD	OVRP/DVRPA
Kirk Prutzman, PhD	OVRP/DVRPA
Roshan Ramanathan, MD	OVRP/DVRPA
David Rouse	OD
Lisa Stockbridge, PhD	OCBQ/DCM
Elizabeth Sutkowski, PhD	OVRP/DVRPA
Claudia Wrzesinski, PhD	OVRP/DVRPA
Hong Yang, PhD	OBE

APPLICANT ATTENDEES

David Greenberg
Corrine Jouquelet-Royer
Alena Khromava
Riyadh Muhammad
Chris Nelson
Patrick O'Neil
Stephen Savarino
Mike Stirr
Francois Verdier

BACKGROUND

BLA 125682/0 was submitted on August 31, 2018, for Dengue Tetravalent Vaccine, Live (DENG VAXIA).

Proposed indication(s): 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. Previous dengue infection can be assessed through a medical record of a previous laboratory confirmed dengue infection or through current serotesting

PDUFA goal date: May 1, 2019

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on February 15, 2019, and issued Advisory Committee Briefing Materials on February 12, 2019.

DISCUSSION

1. Discussion of Substantive Review Issues

a. Product Testing and Release

- i. Establishment of the minimum release specification for virus concentration: We reference the information request dated January 11, 2019, and your response dated February 11, 2019. We will be requesting that you provide the stability data summarized in your February 11, 2019, amendment. We are reviewing your justification for the minimum release specification for virus concentration and will provide feedback after the February 20, 2019, Late Cycle Meeting.

Meeting discussion:

CBER indicated that following review of the February 11, 2019, amendment there are still concerns regarding vaccine stability and product release specifications. CBER informed Sanofi that an IR will be sent within a week. Sanofi stated that they will discuss the issue internally and respond, if possible, or they will wait for CBER's IR.

- ii. Identity testing on final, labeled drug product: We reference the information request dated February 1, 2019. Currently, the BLA does not include an identity test prior to release of each vaccine lot after all labeling operations have been completed as required by 21 CFR 610.14. You have indicated that you plan to submit the assay method and validation information for a "simplified identity test" to be performed at the Swiftwater, U.S. If you are unable to submit the SOP and validation report for the simplified identity test by March 1, 2019, we recommend you consider performing the test at the (b) (4), site using the validated test described in SOP Q_0144050 (i.e., by sending samples of Finished Product lots from Swiftwater to (b) (4)).

Meeting discussion:

Sanofi stated that they intend to submit the SOP and validation report for the simplified identity test to be conducted at the Swiftwater, U.S. site by March 1, 2019.

- iii. Validation of the SOP for residual moisture testing on drug product: We reference the Information Request dated November 29, 2018, in which we asked for a full validation of the residual moisture assay to be conducted on your drug product. You have indicated that you will provide the validation report by the end of March 2019.

Meeting discussion:

Sanofi stated that they intend to meet the date for submitting the validation report.

- iv. Testing on support lots is not complete. CBER has received the (b) (4) [REDACTED] for each of the four dengue serotypes. We are waiting for the shipment of other reagents and samples. Completion of testing is contingent on receipt of reagents and materials needed for the assay. If we learn of any issues from the product testing, the agenda will be modified accordingly.

Meeting discussion:

Sanofi stated that the (b) (4) [REDACTED] were already received by CBER. The vaccine lots are in transit and are expected to be delivered to CBER on February 26, 2019. Sanofi received the CDC permits for shipping the Vero cells on February 20, 2019, and the Vero cells will be sent to CBER in a few weeks.

b. Clinical

- i. Discussion on the proposed indication and review of the Prescribing Information (PI) are ongoing. Labeling meetings have been scheduled, and the target date for sending labeling comments to Sanofi is no later than April 1, 2019.

Meeting discussion:

Sanofi acknowledged.

c. Pharmacovigilance

- i. We would like to discuss with you the feasibility of conducting enhanced pharmacovigilance for detection of cases of severe dengue in vaccinees. Specifically, we would like to discuss using either a) a hospital-based surveillance system, in which enrolled hospitals in Puerto Rico identify hospitalized cases of severe dengue in vaccinees to determine prevaccination serostatus or b) the island-wide, laboratory-based Passive Dengue Surveillance System (PDSS) in Puerto Rico to identify cases of severe dengue in vaccinees to determine prevaccination serostatus. Periodic reports of the findings may be shared with FDA by Sanofi in the Periodic Safety Update Reports. We would also like to discuss alternatives approaches if proposed by Sanofi.

Meeting discussion:

Sanofi asked if CBER is concerned about inadvertent vaccination (of seronegative persons) or effectiveness of the vaccine. CBER indicated that the concern is primarily about identifying cases of inadvertent vaccination of seronegative persons. CBER clarified that the recommendation is for enhanced pharmacovigilance and that Sanofi does not need to conduct a separate postmarketing study. CBER specified that the Health Care Provider (HCP) guide proposed by Sanofi is considered promotional

material, and therefore the HCP guide and the HCP survey will not be part of the pharmacovigilance plan (PVP). CBER and Sanofi agreed to have a follow-up technical call/meeting to discuss the PVP.

2. Discussion of Minor Review Issues

a. CMC

- i. (b) (4) for drug substance manufacture: We reference the information request dated January 11, 2019, in which we asked you to narrow your (b) (4) during the (b) (4) step (currently can vary (b) (4)) and your (b) (4) time ranges (currently can vary from (b) (4)) or explain why such wide (b) (4) and (b) (4) ranges must be used. We are reviewing your justification for retaining these operational ranges submitted in your amendment dated February 11, 2019, and will provide feedback after the February 20, 2019, Late Cycle Meeting.

Meeting discussion:

Sanofi acknowledged.

3. Outstanding Information Requests

- a. 2/14/19: Request to submit a revised lot release protocol template
- b. 2/1/2019: Request regarding the virus identification test for release of the finished product
- c. 12/3/2018: Request for samples, reagents and SOPs for CBER testing
- d. 11/29/2018: Request for validation of the residual moisture method for freeze-dried product

Meeting discussion:

Sanofi acknowledged and indicated that they are expecting to meet the dates to provide the requested information.

4. Discussion of Upcoming Advisory Committee Meeting

Date of AC meeting: March 7, 2019

Date AC briefing package sent under separate cover by CBER's Advisory Committee

Staff: February 12, 2019

Meeting discussion:

Sanofi acknowledged.

5. Risk Management Actions (e.g., REMS)

There is no anticipation of a REMS at this time.

Meeting discussion:

Sanofi acknowledged.

6. Postmarketing Requirements/Postmarketing Commitments

There is no anticipation of PMRs/PMCs at this time.

Meeting discussion:

Sanofi acknowledged.

7. Review Plans

- a. The PI is under review, and the target date for sending labeling comments to Sanofi is no later than April 1, 2019.
- b. We will take an action on this application no later than May 1, 2019.

Meeting discussion:

Sanofi acknowledged.

8. Applicant Questions

Meeting discussion:

Sanofi stated that they don't have any further questions to discuss.

9. Wrap-up and Action Items

- a. CBER restated that they will be sending an IR regarding minimum release specification within a week, and indicated that a resolution of this issue may require additional discussion.
- b. CBER indicated that additional meetings with Sanofi to discuss an enhanced PVP may be necessary. Sanofi stated that they prefer not to have the teleconference during the week of VRBPAC meeting.
- c. CBER stated the Late Cycle meeting summary will be sent to Sanofi within 30 days.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair, and therefore this meeting did not address the final regulatory decision for the application.