



Our STN: BL 125682/0

MID-CYCLE COMMUNICATION SUMMARY

January 18, 2019

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

Dear Mr. Stirr:

Attached is a copy of the summary of your December 20, 2018, Mid-Cycle Communication 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 as soon as possible.

Please include a reference to STN 125682/0 in your future submissions related to Dengue Tetravalent Vaccine (Live, Attenuated) (Dengvaxia).

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

Mid-Cycle Communication Teleconference Summary

Application number: BLA STN 125682/0
Product name: Dengue Tetravalent Vaccine (Live, Attenuated) (Dengvaxia)
Proposed Indication: 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.
Applicant: Sanofi Pasteur, Inc.
Meeting date & time: December 20, 2018, 1:00 – 2:30 PM
Committee Chair: Kirk Prutzman, PhD
RPMs: Ramachandra Naik, PhD and Stephanie Polo

Review Committee Participants:

Wambui Chege, PhD	OBE/DE
Mridul Chowdhury, PhD	OBE/DB
Dino Feigelstock, PhD	OVRP/DVP
Jie He, PhD	OCBQ/DMPQ
Lei Huang, PhD	OBE/DB
Ralph LeBlanc, MD	OVRP/DVRPA
Ramachandra Naik, PhD	OVRP/DVRPA
Stephanie Polo	OVRP/DVRPA
Kirk Prutzman, PhD	OVRP/DVRPA
Hong Yang, PhD	OBE

Other Participants:

Meghna Alimchandani	OBE
Deepa Arya, PhD, MPH, MBA	OBE/DE
Qiao Bobo, PhD	OCBQ/DMPQ
Doran Fink, MD, PhD	OVRP/DVRPA
Richard Forshee, PhD	OBE
Helen Gemignani	OVRP/DVRPA
Marion Gruber, PhD	OVRP
Philip Krause, MD	OVRP
Lucia Lee, MD	OVRP/DVRPA
Robin Levis, PhD	OVRP/DVP
Tsai-Lien Lin, PhD	OBE/DB
Adamma Mba-Jonas, PhD	OBE/DE
Loris McVittie, PhD	OVRP/DVRPA
Laurie Norwood	OCBQ/DMPQ
Roshan Ramanathan, MD	OVRP/DVRPA
Jeff Roberts, MD	OVRP
Nikunj Sharma, PhD	OVRP/DVRPA
Elizabeth Sutkowski, PhD	OVRP/DVRPA

Agenda:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

- a. **Pre-license Inspection/waivers:** The pre-license inspections of the manufacturing sites in (b) (4) (FEI (b) (4)) and (b) (4) (FEI (b) (4)), held in (b) (4) , are still under review. We are not planning on conducting pre-license inspections of your (b) (4) (FEI (b) (4)), Swiftwater, PA, USA (FEI 2518760) or Toronto, Ontario, Canada (FEI 3002888623) sites.

Meeting Discussion:

Sanofi stated that the response to the pre-license inspection questions/items for the (b) (4) site will be submitted on December 31, 2018, and for the (b) (4) site, the response will be submitted on January 18, 2019. CBER acknowledged.

- b. **Product:** We note that the lower limit of the specification for the potency test ((b) (4) \log_{10} CCID₅₀/dose) is the same for release and expiry of Dengvaxia. Given that your stability data indicate the potential for potency loss over the 36-month dating period and given intrinsic potency assay variability, lots released close to or at (b) (4) \log_{10} CCID₅₀/dose may fail to meet the (b) (4) \log_{10} CCID₅₀/dose minimum potency specification throughout the dating period. We recommend that the minimum release specification for potency be increased to ensure, with 95% confidence, that the measured potency will meet the (b) (4) \log_{10} CCID₅₀/dose expiry specification through the 36-month shelf life.

Meeting Discussion:

CBER stated that we are finalizing the Information Request (IR) regarding release specifications for potency. Sanofi acknowledged, and stated that they will submit a prompt response to the IR.

- c. **Risk-Benefit:** Reference is made to the outstanding information request dated December 12, 2018. CBER continues to conduct a benefit-risk assessment for administering Dengvaxia in dengue endemic US territories.

Meeting Discussion:

Please see discussion under item 3 below.

2. Information regarding major safety concerns.

Clinical: With regard to the identified risk of severe dengue among subjects who were seronegative to dengue when they received Dengvaxia and subsequently exposed to a dengue virus, we will continue to work with you on

development of an acceptable risk mitigation strategy, which will include Prescribing Information (PI) that is adequate to ensure clear communication of the risk to health care providers and potentially other measures.

Meeting Discussion:

Please see discussion under item 3 below.

3. Preliminary Review Committee thinking regarding risk management.

A postmarketing study to characterize the risk of administering Dengvaxia in dengue endemic US territories may be required. However, we have not made a decision at this time.

Meeting Discussion:

Regarding a postmarketing study, Sanofi asked if CBER could provide any additional information on what a PMR might include. CBER stated that we will make the determination regarding the need for a PMR after risk-benefit assessment and further deliberations. CBER asked Sanofi what they are planning to do regarding post-licensure surveillance. Sanofi responded that they are not planning to conduct any postmarketing surveillance beyond what was included in the BLA. Sanofi indicated that they are planning to conduct an assessment on risk minimization and to investigate if there is any administration of the vaccine outside of the labeled indication.

Regarding submitting a response to the December 12, 2018, IR, referred to in item 1(c) above, Sanofi indicated that few screening tests are available in Puerto Rico, and the data from these tests will not be available by the date requested in the IR. Sanofi asked if it would be acceptable to CBER if they submit the response to item 4 in the December 12, 2018, IR later than the date requested. CBER agreed with Sanofi's proposal.

Regarding item 2 above, Sanofi asked if CBER has a set timeline to discuss the Dengvaxia Package Insert. CBER stated that a specific timeline has not been set. CBER and Sanofi agreed that it will be important to discuss pertinent labeling changes before the March 7, 2019, VRBPAC meeting.

Regarding a rapid diagnostic test (RDT) for prior dengue infection, CBER asked if the current (b) (4) will be available in Puerto Rico after the May 1, 2019, action due date for the Dengvaxia BLA. Sanofi indicated that they do not plan to seek licensure for the current (b) (4) in U.S. Sanofi clarified that they are (b) (4)

Sanofi indicated that they are also evaluating the current diagnostic tests available in Puerto Rico. CBER noted that there should be a broader discussion regarding sensitivity/specificity as their RDT development proceeds. Sanofi agreed.

CBER asked if Sanofi is planning to present data on the seroprevalence of Zika in Puerto Rico as well as the results of their (b) (4) optimization, including any cross-reactivity with Zika antibodies, at the March 7, 2019, VRBPAC meeting. Sanofi responded that they will include these data if available.

4. Any information requests sent and responses not received.

- a. IR dated 12/3/2018: request for samples, reagents and SOPs for CBER testing
- b. IR dated 12/12/2018: request for a benefit-risk assessment of administration of Dengvaxia in a setting with co-circulation of other flaviviruses
- c. IR dated 12/17/18: request to submit the US health care providers (HCP) guide no later than January 15, 2019

Meeting Discussion:

Sanofi stated that they are on track to submit the SOPs, samples and reagents for CBER testing in early 2019.

5. Any new information requests to be communicated.

None at this time.

Meeting Discussion:

CBER stated that we will send at least one CMC IR regarding release specifications.

CBER informed Sanofi that we will send an IR to include the items discussed during the pre-licensing manufacturing facilities inspections.

6. Proposed dates for the Late-Cycle Meeting (LCM).

- a. The LCM between Sanofi and the review committee is currently scheduled for February 20, 2019, 9:30 AM;
- b. We intend to send the LCM materials to Sanofi by February 18, 2019.

If these timelines change, we will communicate updates to you during the course of the review.

Meeting Discussion:

Regarding the format of LCM, CBER asked Sanofi if they prefer a teleconference or a face-to-face meeting. Sanofi stated that they will inform CBER of their preference soon.

7. The Vaccines and Related Biological Products Advisory Committee meeting is scheduled for March 6 or 7, 2019.

Meeting Discussion:

CBER informed Sanofi that the Vaccines and Related Biological Products Advisory Committee meeting for Dengvaxia is scheduled for March 7, 2019.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.
 - a. Proposed labeling comments: April 1, 2019
 - b. Proposed PMC/PMR (if any): April 1, 2019
 - c. First Action Due: May 1, 2019

Meeting Discussion:

There was no discussion of this item during the meeting.