

Late-Cycle Internal Meeting Summary

Application number: BLA STN 125682/0
Product name: Dengue Tetravalent Vaccine, Live (DENGVAIXIA)
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: January 31, 2019, 10:30 AM – 12:00 PM
Committee Chair: Kirk Prutzman, PhD
Meeting Recorders: Ramachandra Naik, PhD
 Stephanie Polo

Attendees:

Review Responsibility	Committee Member	Attended	Team Leader/ Supervisor	Attended
Chair	Kirk Prutzman, PhD	✓	Elizabeth Sutkowski	✓
RPM	Ramachandra Naik, PhD	✓		
RPM	Stephanie Polo	✓	Rakesh Pandey	
Clinical	Ralph LeBlanc, MD	✓	Lucia Lee	✓
			Roshan Ramanathan	✓
Toxicology	Nabil Al-Humadi, PhD	✓	Dave Green	✓
Toxicology	Claudia Wrzesinski, PhD			
Statistics-Clinical Safety and Assays	Lei Huang, PhD	✓	Tsai-Lien Lin	✓
Statistics-Clinical Efficacy	Mridul Chowdhury, PhD	✓		
CMC and CMC Inspector	Dino Feigelstock, PhD	✓	Robin Levis	
DS and DP release assays	Tao Pan, PhD	✓	Lokesh Bhattacharyya	✓
DS and DP release assays	Simleen Kaur, PhD	✓	James Kenney	
DS and DP release assays	Noel Baichoo, PhD	✓	Muhammad Shahabuddin	✓
LRP and Testing Plan Development	Marie Anderson, PhD	✓	Suzanne Carter	✓
Lot Release Protocol	Cheryl Hulme		Joseph Quander	
CMC, CCIT, Facilities reviewer and inspector	Jie He	✓	Ellen Huang	
			Qiao Bobo	✓
BIMO	Christine Drabick	✓	Dennis Cato	✓
	Malcolm Nasirah	✓		
Advertising/Promotional Labeling	Oluchi Elekwachi	✓	Lisa Stockbridge	✓
Pharmacovigilance	Wambui Chege, PhD	✓	Deepa Arya	✓
			Adamma Mba-Jonas	✓
Benefit-risk assessment	Hong Yang, PhD	✓	Richard Forshee	✓
DMPQ RPM	Marian Ortiz-Rodriguez		James Crim	
OBE Regulatory Coordinator	Lori Austin-Hansberry, MSA, BSN		Steve Anderson	✓
Labeling	Daphne Stewart	✓	Tim Nelle	✓
Electronic Integrity	David Schwab, MSIS		Loris McVittie	✓

Review Responsibility	Committee Member	Attended	Team Leader/ Supervisor	Attended
Consult – Data Integrity	Brenda Baldwin, PhD	✓	Elizabeth Sutkowski	✓

OTHER PARTICIPANTS

Meghna Alimchandani	Sara Gagneten	Jeff Roberts
Cara Fiore	Doran Fink	Maryna Eichelberger
Qun Wang	Craig Zinderman	Carrie Mampilly
Tony Wang	Marion Gruber	Belete Teferedegne
Telba Irony	Laurie Norwood	Sarah Browne
Douglas Pratt	Carmen Collazo	Philip Krause
John Eltermann	Nikunj Sharma	

1.0 BACKGROUND AND PURPOSE

BLA STN 125682/0 was submitted by Sanofi Pasteur, Inc. (Sanofi) on August 31, 2018, and received by CBER on August 31, 2018.

The purpose of this meeting was to:

- discuss progress of the review;
- identify and present any substantive issues/major deficiencies and plans to address substantive issues;
- plan the remainder of the review including dates for further deliverables and interactions;
- agree on the agenda and meeting materials to be communicated to the Applicant prior to the Late Cycle meeting.

2.0 Review Timetable (milestones are in blue)

Review Milestone	Target Due Date
Submitted:	August 31, 2018
Received:	August 31, 2018
First Committee Meeting:	September 13, 2018
Committee Assignment:	September 14, 2018
Filing checklist/reviews complete:	October 9, 2018
Filing Meeting:	October 15, 2018
Filing Action:	October 30, 2018
Draft Lot release protocol and Testing plan:	October 30, 2018
Deficiencies Identified letter:	November 12, 2018
Primary Draft Reviews & Reviewer Reports Due (4 days prior to Mid-Cycle meeting):	November 30, 2018
Mid-Cycle Meeting (Internal):	December 6, 2018
Mid-cycle communication with applicant:	December 20, 2018
Internal Late cycle meeting	January 31, 2019
Late cycle briefing pkg & VRBPAC briefing pkg to applicant (20 days before VRBPAC):	February 15, 2019

Review Milestone

Final draft primary reviews with
supervisory concurrence:
(upload not required), due by LC meeting

Late cycle meeting:

(At least 12 days before VRBPAC)

PMC/PMR Determination:

(Notify/involve OVRP SWG Rep)

PLI Inspections completed:

BIMO Inspections completed:

VRBPAC Meeting:

PeRC Briefing materials due:

Press release (contact Maureen Hess):

PeRC Meeting:

Employee Officer list memo:

Lot release protocol and Testing plan
finalized:

Final reviews & addenda signed &
uploaded:

Notify OCOD of pending approval:

Labeling Comments to Applicant:

Notify Applicant of PMC/PMR:

Action Due Date (ADD):**Target Due Date**

February 20, 2019

February 20, 2019

March 2, 2019

March 2, 2019

March 2, 2019

March 7, 2019

March 13, 2019

March 15, 2019

March 27, 2019

April 1, 2019

April 1, 2019

April 1, 2019

April 1, 2019

April 1, 2019

April 1, 2019

May 1, 2019

Meetings scheduled:

Milestone meetings	
First Committee Meeting	September 13, 2018, 11:00 AM – 12:00 PM
Filing Meeting	October 15, 2018, 1:00 – 2:30 PM
Internal Mid-Cycle meeting	December 6, 2018, 11:00 AM – 12:30 PM
Mid-Cycle communication	December 20, 2018, 1:00 – 2:30 PM
Internal Late Cycle meeting	January 31, 2019, 10:30 AM – 12:00 PM
Late Cycle meeting with Sanofi	February 20, 2019, 9:30 AM – 11:00 AM

Other meetings	
BIMO site selection	September 11, 2018, 1:00 – 2:00 PM
Discussion of DVP-DBSQC review teams' review responsibilities, product testing and LRP	October 16, 2018, 10:30 AM – 12:00 PM
CBER-Sanofi meeting to discuss on updates on their (b) (4)	November 14, 2018, 1:00 – 2:30 PM
November monthly committee meeting	November 15, 2018, 1:00 – 2:30 PM
Team/OVRP meeting regarding Sanofi's (b) (4)	November 19, 2018, 11:00 – 12:00 PM

CBER-Sanofi meeting to discuss DS/DP testing/reagents	November 27, 2018, 10:00 - 11:00 AM
Dengvaxia VRBPAC briefing document	December 20, 2018, 3:00 – 4:00 PM
Dengvaxia Package Insert review	January 15, 2019, 10:00 AM – 12:00 PM
Dengvaxia Package Insert review	January 17, 2019, 9:30 AM – 12:30 PM
Dengvaxia Package Insert review	January 24, 2019, 10:00 AM – 12:30 PM
Dengvaxia Package Insert review	January 28, 2019, 11:00 AM – 12:30 PM
Dengvaxia Package Insert review	January 29, 2019, 10:00 AM – 12:30 PM
Dengvaxia VRBPAC rehearsal	February 20, 2019, 1:00 – 3:30 PM
Dengvaxia VRBPAC rehearsal	February 28, 2019, 1:00 – 4:00 PM
Dengvaxia VRBPAC rehearsal	March 5, 2019, 11:00 AM – 1:00 PM
March monthly committee meeting	March 25, 2019, 1:00 – 2:30 PM
PeRC review	March 27, 2019, 9:00 AM – 12:00 PM

3.0 Discussion:

3.1 Reports from reviewers

Product - CMC (Dino Feigelstock)

- Review is almost complete. The major outstanding issues include:
 - Establishment of the minimum release specification for virus concentration: The January 11, 2019 IR is outstanding, and the response from Sanofi is expected on February 11, 2019.
 - Identity testing for the finished product: Sanofi plans to simplify the existing virus concentration/identity test, but will not be able to submit the SOP and validation information prior to the DENG VAXIA BLA action due date. An identity test on the finished product needs to be in place at the time of approval. An IR will be sent to Sanofi.
- Date the review will be completed: February 28, 2019

Product Quality – LRP and Testing Plan Development (Marie Anderson)

- Pending IR for in-support testing samples and reagents; shipment estimated to arrive on February 6, 2019.
- A revised LRP template has been routed for review; an IR for a revised LRP template to address additional changes will be sent. The reviewer noted that a change to the minimum release specification for virus concentration will require the LRP to be revised.
- Date the review will be completed: February 28, 2019

Product Quality – Analytical Method and Validation (Tao Pan)

- Review of assay for residual moisture has not been completed;
- Outstanding November 29, 2018 IR for additional validation data on moisture assay; response expected by the end of March 2019;
- Date the review will be completed: April 15, 2019

Product Quality - Microbiological assay - sterility and endotoxin (Simleen Kaur)

- Review completed; memo uploaded on November 20, 2018

Product Quality - Potency/Identity and (b) (4) content (Noel Baichoo)

- Review of Sanofi's response to January 11, 2019 IR regarding the potency assay is pending;
- Date the review will be completed: February 15, 2019

Pharmacology - Toxicology (Nabil Al-Humadi and Claudia Wrzesinski)

- All toxicology studies have been reviewed; draft review memo completed;
- The package insert has been reviewed, and suggested edits have been provided regarding reproductive toxicity in mice. At doses of 6.5 and 8 log₁₀ CCID₅₀ of CYD Dengue vaccine (about 30 and 1000 times the human dose, respectively), maternal toxicity, including dose dependent reduced maternal body weight gain and/or food consumption, was observed which was associated with increased postimplantation loss, as well as reduced fetal body weight (only at 8 log₁₀ CCID₅₀ of CYD Dengue vaccine); this issue will be discussed and resolved during the review of the package insert.
- Date the review will be completed: February 28, 2019

Clinical (Ralph LeBlanc)

- Draft review memo completed;
- REMS not needed;
- Date the review will be completed: April 15, 2019

Benefit-Risk assessment (Hong Yang)

- Outstanding December 12, 2018 IR regarding benefit-risk assessment of the administration of DENG VAXIA in a setting with co-circulation of other flaviviruses; Sanofi plans to include an analysis of two screening tests that are available in Puerto Rico to assess their use for pre-vaccination screening; response to the IR is expected in early February 2019.
- Date the review will be completed: March 31, 2019

Statistics – Clinical Safety and Assays (Lei Huang)

- Outstanding January 11, 2019 IR regarding minimum release specification for virus concentration; response expected February 11, 2019
- Date the review will be completed: February 14, 2019

Statistics – Clinical Efficacy (Mridul Chowdhury)

- Each pivotal study (CYD14 and CYD15) met the primary objective of vaccine efficacy. For secondary objectives, the efficacy by serotype met the lower bounds, except for serotype 2.
- Discussions are ongoing regarding immunebridging to subjects 18-45 years.
- Date the review will be completed: January 31, 2019

Epidemiology/Pharmacovigilance (Wambui Chege)

- Review of the Risk Management Plan and international postmarketing data is ongoing
- International postmarketing experience in the package insert will be revised
- Response to request for Australia Therapeutic Goods Association to share information regarding postmarketing experience with DENG VAXIA is outstanding.
- OBE agrees that a REMS and a PMR regarding the severe dengue safety signal are not feasible. OBE is considering options for enhanced pharmacovigilance for severe dengue using hospital-based surveillance or existing surveillance systems in Puerto Rico. OBE will discuss these options with Sanofi at the February 20, 2019, Late Cycle Meeting.
- Date the review will be completed: March 31, 2019

DMPQ Reviewer – CMC, CCIT, Facilities, Inspector (Jie He)

- The response to the November 9, 2018 IR submitted in Amendment 13 is under review.
- The two pre-license inspections for (b) (4) facilities were completed on (b) (4), respectively, and 483s were issued for both sites. Sanofi submitted the responses to the 483s on December 27, 2018, and January 17, 2019, respectively. Review of the responses is currently ongoing.
- Plan to request that Sanofi submit the 483 responses in an amendment to the BLA.
- Date the review will be completed: February 28, 2019

BIMO (Christine Drabick and Malcolm Nasirah)

- BIMO inspections at two clinical sites in Puerto Rico for Study CYD15 have been completed.

- BIMO inspections which were scheduled to be performed in January 2019 in Indonesia and the Philippines for Study CYD 14 and in Brazil for Study CYD 15 have been rescheduled. The inspections in Indonesia and the Philippines are now scheduled for February 25-March 1, 2019, and the inspection in Brazil is scheduled for March 11-15, 2019.
- Date the review will be completed: within 30 days after receipt of all Establishment Inspection Reports (EIRs).

3.2 Upcoming timeline/deadlines

- The Chair informed the review team that Late Cycle meeting materials and the VRBPAC briefing documents are due to Sanofi by February 15, 2019.

3.3 Issues to be included on the agenda for the LCM with the Applicant

- Virus identification test for the finished product

4.0 Action items

- a. Schedule additional labeling meetings
- b. Schedule PeRC paperwork preparatory meetings
- c. Finalize agenda for the Late Cycle meeting with Sanofi
- d. Finalize/send the IR from DVP regarding the simplified virus identification/concentration test
- e. Send an IR for Sanofi to submit the 483 responses as an amendment to the BLA.