

Mid-Cycle Meeting Summary

Application number: BLA STN 125682/0
Product name: Dengue Tetravalent Vaccine (Live, Attenuated) (DENGVAIXA)
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 6, 2018, 11:00 AM – 12:30 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	✓	Steve Rubin	✓
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	✓
Consult – Data Integrity	Brenda Baldwin, PhD		Elizabeth Sutkowski	✓

OTHER PARTICIPANTS

Carmen Collazo

Maryna Eichelberger

Qun Wang

Sarah Browne

Cara Fiore

Sara Gagnetten

Laurie Norwood

Meghna Alimchandani

Barbee Whitaker

Belete Teferedegne

Carrie Mampilly

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Doran Fink

Philip Krause

Jeff Roberts

Robin Levis

Tony Wang

Yosefa Hefter

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 the progress of the review; to identify and present any substantive issues/major deficiencies and plans to address substantive issues; to plan the remainder of the review including dates for further deliverables and interactions; and agree on the material to be communicated in the Mid-Cycle Communication telecon and determine which reviewers will participate in the MCC telecon to present their issues.

2.0 Review Timetable (milestones are in blue)

Review Milestone

Submitted:

Received:

First Committee Meeting:

Committee Assignment:

Filing checklist/reviews complete:

Filing Meeting:

Filing Action:

Draft Lot release protocol and Testing plan:

Deficiencies Identified letter:

Primary Draft Reviews & Reviewer Reports

Due (4 days prior to Mid-Cycle meeting):

Mid-Cycle Meeting (Internal):

Mid-cycle communication with applicant:

Internal Late cycle meeting

Late cycle briefing pkg & VRBPAC briefing
pkg to applicant (20 days before VRBPAC):

Final draft primary reviews with
supervisory concurrence:

(upload not required), due by LC meeting

Late cycle meeting:

(At least 12 days before VRBPAC)

Target Due Date

August 31, 2018

August 31, 2018

September 13, 2018

September 14, 2018

October 9, 2018

October 15, 2018

October 30, 2018

October 30, 2018

November 12, 2018

November 30, 2018

December 6, 2018

December 20, 2018

January 31, 2019

February 15, 2019

February 20, 2019

February 20, 2019

Review Milestone

PeRC Briefing materials due:
 PeRC Meeting:
 PMC/PMR Determination:
 (Notify/involve OVRP SWG Rep)
 PLI Inspections completed:
 BIMO Inspections completed:
 VRBPAC Meeting:
 Employee Officer list memo:
 Press release (contact Maureen Hess):
 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

March 13, 2019
 March 27, 2019
 March 2, 2019

 March 2, 2019
 March 2, 2019
 March 6, 2019
 April 1, 2019
 March 15, 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 development of a (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 development of (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 rehearsal	January 28, 2019, 11:00 AM – 1:30 PM
Dengvaxia VRBPAC rehearsal	February 11, 2019, 11:00 AM – 1:30 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

Reports and Discussion:

The Chair presented a brief overview of the submission followed by updates from individual reviewers

1. Reviewer Reports

Product - CMC (Dino Feigelstock)

- No substantial issues identified; no outstanding IR(s); some sections from modules 3.2.S, 3.2.P, and 5.3.5.4. have not been completely reviewed
- Date the review will be completed: January 21, 2019

Discussion:

The Product reviewer indicated that the minimum release potency specification is the same as the expiry specification. He indicated that clarification is needed from the Applicant if there any clinical data proving the efficacy of the vaccine at potencies lower than the current expiry potency. The CMC team will further discuss to determine if an IR is to be sent, or to include the request in the Mid-Cycle Communication Telecon agenda.

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

- Review complete; outstanding IR for in-support testing samples and reagents (requested receipt in early January 2019); LRP template routed to the CMC reviewers; CBER Laboratory Testing Plan drafted.
- Date the review will be completed: January 30, 2019

Discussion:

The reviewer discussed that if the product release specification(s) are changed, then the LRP needs to be revised. The Product reviewer will update the Product Quality reviewer if any release specifications change.

Product Quality – Analytical Method and Validation (Tao Pan)

- No issues identified; review of the few assays (appearance, residual moisture, appearance after dissolution, (b) (4)) has not been completed since no SOPs have been provided for (b) (4) assays, and residual moisture assay was not validated; SOPs were provided in Amendment 12 (11/20/2018), but no validation data were provided for the moisture assay; an IR was sent on 11/29/2018.

- Date the review will be completed: December 30, 2018

Discussion:

The reviewer stated that he is waiting for English versions of the SOPs for testing/reagents.

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

- No issues identified;
- Review completed; memo uploaded on November 20, 2018.

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

- No issues identified; 11/30/2018 outstanding IR regarding incubation times for steps in the potency assay
- Date the review will be completed: December 31, 2018 (pending receipt of response to the 11/30/2018 IR)

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

- All toxicology studies have been reviewed; no issues identified; no outstanding IRs; package insert not yet reviewed.
- Date the review will be completed: January 31, 2019

Discussion:

The reviewers informed that there are no issues regarding general toxicity, and reproductive toxicity in rabbits. However, study reports of reproductive toxicity in (b) (4) mice (No. SP0056 DV1014) showed an imbalance in post-implantation loss in mice as well as maternal toxicity. The reviewers stated that these issues may be discussed during the review of DENG VAXIA package insert.

Clinical (Ralph LeBlanc)

- Review areas not completely reviewed to date are *Overview of Safety (ISS)* and *Overview of Efficacy (ISE)*; risk management issues will be jointly decided between clinical reviewer and risk-benefit reviewer. The major issue at this stage [as of November 15, 2018] is the potential impact of available in vitro diagnostic testing for dengue in PR and its impact on potential safety risk of severe disease if individuals who are negative for prior dengue infection cannot be identified with sufficient sensitivity and specificity by available serological tests.
- No outstanding IR(s)
- Date the review will be completed: January 27, 2019

Discussion:

The reviewers presented the summary of the pivotal clinical study reports.

Benefit-Risk assessment (Hong Yang)

- The benefit of DENG VAXIA clearly outweighs the risk for the target population with confirmed prior dengue infection.
- There is question on whether the performance of current available RDT is sufficient to correctly identify the seropositive individuals. Especially, we have concern about the false positive results due to antibody assay for Dengue Fever cross-reactive with other flavivirus (Yellow Fever, Japanese encephalitis, West Nile viruses, and Zika virus). We would like to request for additional information on benefit-risk assessment of vaccination of DENG VAXIA at the setting with co-circulation of other flavivirus based on performance (sensitivity, specificity and cross-reactivity) of potential pre-vaccination screening tests.
- Date the review will be completed: January 21, 2019

Discussion:

The reviewer indicated that she agrees with the edits (refined language) to her request for additional information regarding performance of the benefit-risk assessment.

Statistics – Clinical Safety and Assays (Lei Huang)

- Reviews not completed – ISS, additional safety analysis with NS1 results, qualification report for NS1 assay, stability data and release specifications for viral concentration;
- Issues: Some non-serious AEs have missing severity; some SAEs have partial starting dates, and the SAP states that missing or partial missing dates will not be imputed. It is unclear how the summary of SAEs by period (Active phase, HP/SEP) was generated.
- The plan to address missing AE grades is to request a manual review of the nature of the AEs with missing grade by a clinical reviewer. If the AEs with missing grades are trivial in nature, this will likely not impact safety review. In addition, an analysis of the worst-case scenario can be performed; an IR may need to be sent to the applicant requesting clarification on how partial dates were handled.
- No outstanding IRs
- Date the review will be completed: January 18, 2019

Discussion:

The reviewer stated that he does not need additional information from the Applicant (No IRs).

Statistics – Clinical Efficacy (Mridul Chowdhury)

- Reviews not completed – exploratory/ supportive analyses as priority/focus is given on the primary endpoints analyses of CYD14 and CYD15
- Issues: For licensure consideration, all randomized subjects <9 years age in CYD 14 were excluded from analysis, thereby raising the concern over the extent of effect such exclusion can have on the study's conclusion. How does the Applicant plan to deal with and address this issue? The applicant may consider providing convincing arguments to mitigate the concern.
- Date the review will be completed: January 31, 2019

Discussion:

The reviewer indicated that he has some concerns regarding how excluding subjects <9 years of age in CYD 14 affects the study's conclusion. These issues will be discussed during the review of DENG VAXIA package insert.

Epidemiology/Pharmacovigilance (Wambui Chege)

- Review ongoing; 11/30/2018 outstanding IR regarding details on the Guide for Health Care Providers and request to clarify discrepancies; IR to be sent - request to Australia Therapeutic Goods Association regarding postmarketing experience with Dengvaxia
- Issues: Ongoing evaluation of the need for additional postmarketing measures to quantify and mitigate the risk of vaccinating seronegative individuals; planned ad hoc discussion regarding IRs and pharmacovigilance recommendations
- Date the review will be completed: February 28, 2019

Discussion:

The Epidemiology/Pharmacovigilance reviewer informed that the Pharmacovigilance planning will be discussed at the December 12, 2018, meeting scheduled with OBE-OVR teams to discuss the IR to be sent to the Australian Therapeutic Goods Administration regarding their post-marketing regulatory decisions and post-marketing experience with DENG VAXIA. In the same meeting, the rationale for a PMR/PMC plan will be discussed.

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

- Reviewed all sections, but inspections should be completed for completing the review memo; no outstanding IR(s)
- The two pre-licensure inspections will take place from December 3- 18, 2018.
- Date the review will be completed: January 31, 2019

Discussion:

The Team Leader for the DMPQ reviewer stated that the reviewer is out for inspections. Inspection at the first location closes on Monday (December 10, 2018). The reviewer has some concerns/questions regarding lyophilization process, and will address those during the inspections or as part of the review process.

BIMO (Christine Drabick and Malcolm Nasirah)

- No issues; no outstanding IR(s)
- BIMO inspections at two clinical sites in Puerto Rico for Study CYD15 are completed
- BIMO inspections at clinical sites in Indonesia and Philippines for Study CYD14 are scheduled to be conducted January 4-26, 2019. One inspection for Study CYD15 in Brazil is scheduled for January 4-19, 2019.
- Date the review will be completed: within 30 days after receipt of all Establishment Inspection Reports (EIRs).

2. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.

- VRBPAC is scheduled for March 6 or 7, 2019.

3. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

- CBER has not made a decision on a post-marketing risk management plan at this time.

4. National Drug Code (NDC) assignments to product/packaging (excludes devices).

- Process initiated.

5. Proper naming convention.

- Proper name for DENGAXIA is being discussed

6. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

See Reviewer reports discussion above.

Review

7. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones.

- Late Cycle meeting with the Applicant: February 20, 2019
- VRBPAC meeting: March 6 or 7, 2019
- Labeling discussions: meetings will be scheduled

8. Establish a labeling review plan and agree on future labeling meeting activities.

- Labeling meetings will be scheduled.

Confirm, as applicable

9. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

Complete

10. New facility information is included in the application, requiring implementation of regulatory job aid [JA 910.01: Manufacturing Facility Data Entry](#). If not complete, indicate date it will be completed.

Complete

11. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

- Complete.
- Request for in-support testing samples and reagents has been sent (requested receipt in early January 2019)
- LRP template routed to the CMC reviewers
- CBER Laboratory Testing Plan drafted

12. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid [JA 900.01: Unique Ingredient Identifier \(UNII\) Code](#) for additional information.

- Process initiated

13. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision. Note: Remind the Review Committee that PeRC forms need to be submitted two weeks in advance of scheduled PeRC meeting.

- PeRC briefing materials due: March 13, 2019
- PeRC Meeting: March 27, 2019
- PeRC paperwork preparatory meetings will be scheduled.

14. Action Items:

- a. Scheduling labeling meetings

- b. Scheduling PeRC paperwork preparatory meetings
- c. Discussion to determine if PMC/PMR required
- d. Mid-Cycle Communication telecon agenda

15. For applications subject to the PDUFA/BsUFA Programs:

- a. Teams will further discuss regarding the items to be included in the Mid-Cycle Communication telecon agenda.

Mid-Cycle Communication Agenda

1. Any significant issues/major deficiencies 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.
 - 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.
 - 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.
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.
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.
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

5. Any new information requests to be communicated.

None at this time.

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.

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