

Application Type	Original BLA
STN	125682/0
CBER Received Date	Aug 1, 2018
PDUFA Goal Date	May 1, 2019
Division / Office	DVP /OVRR
Committee Chair	Kirk Prutzman
Project Manager	Ramachandra Naik
Priority Review	Yes
Reviewer Name(s)	Lei Huang
Review Completion Date / Stamped Date	
Concurrence	Tsai-Lien Lin Branch Chief, Vaccine Evaluation Branch DB, OBE
	John Scott Division Director, Division of Biostatistics OBE
Applicant	Sanofi Pasteur, Inc.
Established Name	Dengue Tetravalent Vaccine (Live, Attenuated)
Trade Name	DENGVAXIA
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Live, attenuated, chimeric dengue virus (serotypes 1, 2, 3 and 4)
Dosage Form(s) and Route(s) of Administration	Suspension for injection (0.5 mL) supplied as a lyophilized powder to be reconstituted with the supplied diluent; subcutaneous injection
Dosing Regimen	The 3-dose immunization series consists of a 0.5 mL subcutaneous injection administered at 6-month intervals (Month 0, 6, and 12)
Indication(s) and Intended Population(s)	Dengvaxia is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

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1. Executive Summary

Sanofi Pasteur submitted the original Biologics License Application (BLA 125682) for CYD Dengue Vaccine (Dengvaxia). CYD dengue vaccine is a tetravalent, live attenuated viral vaccine indicated for active immunization for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. The potency and immunogenicity assays were validated and reviewed under IND 11219. This memo covers only the statistical review of the qualification report of the NS1 (non-structural protein 1 of the dengue virus) assay, as well as the stability data supporting release specifications.

For the NS1 assay, while the qualification report appears to be acceptable, a formal validation of the assay was not performed. I defer to the product and clinical reviewer regarding the acceptability of the qualification report in lieu of a validation report. For the stability analysis, the statistical methods used are generally appropriate, and most conclusions appear to be consistent with analysis results. I consider the proposed lower limit of release specifications to be acceptable if the end-of-expiry dose ($(b) (4) \log_{10}$ CCID₅₀/dose) is acceptable. However, it is unclear if the end-of-expiry dose claimed by the applicant is acceptable because there is limited information regarding the immune response for subjects receiving doses at or below $(b) (4) \log_{10}$ CCID₅₀/dose. Therefore, I defer to the clinical and product reviewers regarding acceptability of the end-of-expiry dose.

2. Regulatory Background

As no immunological correlate of protection was established, the efficacy of the CYD dengue vaccine compared to placebo has been assessed in endemic areas in one proof of concept Phase IIb monocenter study (CYD23 conducted in Thailand in children 4 to 11 years) and 2 large-scale Phase III studies performed in 10 countries of southeast Asia Pacific (CYD14, in children and adolescent aged 2 to 14 years) and Latin America (CYD15, in children and adolescent aged 9 to 16 years).

During the first year of the Hospital Phase in Study CYD14, there was an imbalance and a trend towards a higher risk of hospitalized symptomatic VCD in the youngest vaccine recipients in CYD14 (subjects aged 2 to 5 years at enrollment). This imbalance, however, was not observed in older age groups. The observation of an imbalance in the occurrence of hospitalized dengue cases in the youngest age group during the first year of the Hospital Phase has been interpreted by some within the scientific community as a possible indication of an increased risk of dengue hospitalization or severe dengue illness in individuals who have not been exposed to dengue prior to being vaccinated with CYD dengue vaccine. This hypothesis cannot be adequately evaluated with existing data from the CYD dengue VE studies, because pre-vaccination samples were only obtained for a small proportion of participants and because the incidence of dengue hospitalization or severe dengue is much lower than the incidence of any symptomatic VCD, resulting only in partial and largely imprecise estimates of the risk according to prior exposure to natural dengue infection. Nevertheless, blood samples were collected for all study

participants approximately 1 month after the third injection of the CYD dengue vaccine or placebo, i.e., at M13. Efforts were made by the applicant to classify the baseline dengue serostatus of subjects using blood samples collected at this time point. The PRNT assay is not suitable for this purpose because the assay is directly affected by the immune responses induced by the vaccine. Sanofi Pasteur has leveraged an assay originally developed at the (b) (4) which measures total immunoglobulin G (IgG) antibodies against the non-structural protein 1 (NS1) of the dengue virus by Enzyme Linked Immunosorbent Assay (ELISA). It is expected that previous exposure to the CYD dengue vaccine is not likely to induce meaningful levels of antibody against the dengue NS1 protein. The application of the Dengue anti-NS1 IgG ELISA to M13 samples is therefore useful for expanding the existing data on both vaccine efficacy and potential risk of dengue hospitalization and/or severe dengue according to baseline serostatus.

No validation report of the NS1 assay was submitted in the original BLA. In the November 1, 2018 Information Request (IR) response, the applicant stated that they have performed extensive qualification studies to evaluate specificity, accuracy, linearity/dilutability, precision, limit of detection (LOD)/ lower limit of quantitation (LLOQ) and stability of the method for its intended purpose in alignment with ICH Q2(R1) guidelines. Therefore, the applicant does not intend to validate the NS1 assay. The qualification report is thus reviewed in lieu of the validation report in this memo.

During the review, the chemistry, manufacturing and control (CMC) reviewer noted that the release specification and the end-of-expiry (EOE) specification are the same for drug product concentration (potency), as the applicant claimed that there was no degradation over time. However, the CMC product reviewer noticed that the concentration at EOE are numerically lower than that at release for every stability lot, and hence requested a statistical review. The statistical review of the stability data is also covered in this memo.

3. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

3.1 Review Strategy

This statistical review focused on the qualification report of NS1 IgG ELISA assay, assessment of dengue NS1 IgG ELISA for dengue serostatus classification, and the stability data of drug product potency.

3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

BLA 125682/0.0 Submitted 08/31/2018

Module 3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications

3.2.P.5.6 Justification of Specifications

Module 3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

3.2.P.8.3 Stability Data

Module 5.3.5.4 Other Study Reports


5.3.5.4 ns1 – NS1

Inter Laboratory Standardisation Methods Quality Assurance
Appendix 11 Assay Techniques and Standard References
BLA 125682/0.10 Submitted 11/01/2018
Module 1.11.4 Multiple Module Information Amendment
Multiple Module Information Amendments
BLA 125682/0.22 Submitted 02/11/2019
Module 1.11.1 Quality Information Amendment
Quality Information Amendment
BLA 125682/0.30 Submitted 03/18/2019
Module 1.11.1 Quality Information Amendment
Quality Information Amendment
Q_0637198 – DENGUE VACCINE – FILED PRODUCT STAGE – SINGLE DOSE
– STUDY REPORT OF DETERMINATION OF LIMITS AT RELEASE
(T0) ON THE INFECTIOUS TITRATION ON (b) (4)
BLA 125682/0.48 Submitted 04/24/2019
Module 1.11.1 Quality Information Amendment
Quality Information Amendment


4. DISCUSSION OF INDIVIDUAL STUDIES

4.1 Qualification Report for the NS1 IgG ELISA

The Dengue NS1 IgG ELISA method is used to quantitate IgG antibodies in human serum against the Non-Structural Protein 1 (NS1) from four serotypes of Dengue virus (Serotypes 1, 2, 3 and 4). (b) (4)



(b) (4)




(b) (4)

Reviewer Comments

- 1. It was unclear what statistical model was used to evaluate overall repeatability and intermediate precision for the NSI assay. Nevertheless, precision estimates based on different ANOVA models are likely to meet the acceptance criteria since the applicant's precision results were well within the acceptance criteria. I fit a mixed model including sample ID as a fixed effect and analyst, run within analyst, and date as random effects. The point estimates of repeatability and intermediate precision were (b) (4)*


(b) (4)



4.2 Assessment of Dengue NS1 IgG ELISA for Dengue Serostatus Classification

The primary objective was to evaluate the suitability of the method for its application to classify dengue serostatus based on NS1 antibody measurement and determine the thresholds to identify dengue unexposed individuals from dengue exposed individuals.

(b) (4)



4.3 Stability

The applicant conducted a stability study of three industrial batches (b) (4) (b) (4)) to evaluate the stability of drug product manufactured in (b) (4) site under real-time storage condition (36 months at $+5^{\circ}\text{C}\pm 3^{\circ}\text{C}$) and accelerated conditions (b) (4) (b) (4)). No significant relationship between the duration of storage at $+5^{\circ}\text{C}\pm 3^{\circ}\text{C}$ and the variation of virus concentration was detected based on statistical analysis. A significant decrease was observed on virus concentration for all serotypes and (b) (4) batches over (b) (4) except for (b) (4) for serotype 1 at (b) (4) . At (b) (4) , no significant relationship between the duration of storage for (b) (4) and the variation of virus concentration was observed. Based on these results, the applicant concluded that the vaccine stability supports the claimed shelf-life.

The drug product potency specifications were initially set as (b) (4) \log_{10} CCID₅₀/dose and (b) (4) \log_{10} CCID₅₀/dose for each serotype. The applicant claimed that the criteria were supported by clinical studies. In Study CYD12, the batch (b) (4) formulated at (b) (4) ranged from (b) (4) \log_{10} CCID₅₀/dose at the time of injection with a mean value for the 4 serotypes at (b) (4) \log_{10} CCID₅₀/dose. Based on the analysis results of the immune response (i.e. seroconversion rates and geometric mean titers) in CYD12, the applicant concluded that subjects who received batch (b) (4) showed similar results as subjects receiving $\sim 5.0 \log_{10}$ CCID₅₀/dose for each serotype, thus demonstrating the immunogenicity of CYD dengue vaccine when the virus concentration is close to (b) (4) \log_{10} CCID₅₀/dose. Due to the limited data showing a non-significant difference between (b) (4) and 5/5/5/5 lots and the variability in immunogenicity responses, a safety margin of (b) (4) \log_{10} CCID₅₀/dose is considered significant because of both process and analytical method variability ((b) (4) \log_{10} CCID₅₀/dose), resulting in a lower limit of (b) (4) \log_{10} CCID₅₀/dose.

An IR was sent to the applicant on March 1, 2019, requesting additional information on setting the end-of-expiry potency based on Study CYD12, given that in the clinical study report, the applicant concluded in part that in general, the lowest seropositivity rates and GMTs for all serotypes, except for serotype 4, were observed in Group 3 ((b) (4) group). In addition, the agency noted that a failure to demonstrate a decay slope significantly different from zero does not prove that a product is stable through the dating period. Since the applicant referred to a stability study on (b) (4) additional lots in the response to the January 11, 2019 IR, a request for stability data from the (b) (4) additional lots was also included in the March 1, 2019 IR.

In the IR response, the applicant stated that there was a trend for higher seropositivity for all 4 dengue serotypes after 3 doses with the 5/5/5/5 formulation as compared with the (b) (4) formulation, but there was an evident overlap of the confidence interval. As for GMTs, the point estimates for serotypes 2 and 3 were higher for the 5/5/5/5 formulation than for the (b) (4) formulation, but not significantly so. The geometric mean titer (GMT) point estimates for serotypes 1 and 4 were close to identical. Overall, the applicant concluded that the data suggested that the responses were close to reaching a

plateau with the 5/5/5 formulation, given the proximity of the immune response parameters between the two formulations.

The applicant also provided a statistical report of stability analysis with data from (b) (4) batches. A significant decrease of the virus concentration between the release and the 36-month time-point was observed for serotype 1, while no significant degradation in virus concentration throughout 36 months was detected for serotypes 2, 3, and 4. Therefore, the applicant proposed to implement an action limit of (b) (4) \log_{10} CCID₅₀/dose at release in order to meet the low acceptance limit at the end of shelf life with 95% confidence.

Reviewer Comments

Poolability of stability data from the (b) (4) batches was evaluated using a significance level of (b) (4), following the ICH Q1E guideline. Although the degradation slopes for serotypes 2, 3 and 4 were not statistically significant, as the applicant claimed, failure to demonstrate a decay slope significantly different from zero may result from a lack of power due to the small number of lots included in the analysis. I performed additional analysis to calculate a conservative margin to compensate for potential degradation over 36 months, the uncertainty of the estimate of the degradation slope, as well as assay variability, based on the (b) (4) batches. Roughly, increments of (b) (4) \log_{10} CCID₅₀/dose are needed for serotypes 1, 2, 3, and 4, respectively. Therefore, conditional on the acceptability of the dose of 4.5 \log_{10} CCID₅₀/dose as the end-of-expiry dose, setting the lower limit of release specification at (b) (4) \log_{10} CCID₅₀/dose above the end-of-expiry potency, i.e. (b) (4) \log_{10} CCID₅₀/dose, will ensure that lots will meet the end-of-expiry specification at the end of shelf life.

An additional IR was communicated to the applicant on April 19, 2019, requesting the applicant to set the lower limit of release specification as (b) (4) \log_{10} CCID₅₀/dose. On April 24, 2019, the applicant replied to the IR and agreed to revise the lower limit of release specification from (b) (4) \log_{10} CCID₅₀/dose to (b) (4) \log_{10} CCID₅₀/dose. The revision of the common technical document (CTD) sections and the lot release protocol will be submitted as a post approval commitment.

5. CONCLUSION

For the NS1 assay, while the qualification report appears to be acceptable, a formal validation of the assay was not performed. I defer to the product and clinical reviewer regarding the acceptability of the qualification report in lieu of the validation report. For the stability analysis, the statistical methods used are generally appropriate, and most conclusions appear to be consistent with the analysis results. Assuming that the end-of-expiry dose (4.5 \log_{10} CCID₅₀/dose) is acceptable, I consider the proposed lower limit of release specifications acceptable. However, it was unclear if the end-of-expiry dose claimed by the applicant is acceptable because there is limited information regarding the immune response for subjects receiving doses at or below (b) (4) \log_{10} CCID₅₀/dose. Therefore, I defer to the clinical and product reviewers regarding the acceptability of the end-of-expiry dose.