



CBER REGULATORY REVIEW MEMORANDUM

Date 20 November, 2018

From Simleen Kaur
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biological License Application (BLA) Submission Tracking Number 125682/0

Subject BLA: Review of Sterility and Endotoxin Test Method Qualifications for CYD Dengue Vaccine

Through James L. Kenney, D.Sc., Chief, LMIVTS
Maryna Eichelberger, Ph.D., Director, DBSQC

Applicant Sanofi Pasteur (Sanofi)

Product CYD Dengue Vaccine (Dengvaxia)

Biological License Application Submission Tracking Number (STN) 125682/0

Submission Received by CBER 31 August, 2018

Review Completed 20 November, 2018

Material Reviewed

Method qualifications for sterility and endotoxin tests performed on Dengvaxia (b) (4) drug product (DP) and diluent (0.4% NaCl₂) and information request responses received 03 October and 01 November of 2018 were reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds the sterility and endotoxin test methods were qualified in accordance with (b) (4), respectively and the product matrixes for (b) (4) DP and NaCl₂ of Dengvaxia were demonstrated to be suitable for the intended test methods.


Background

On 31 August, 2018, Sanofi submitted this BLA for Dengvaxia, a tetravalent, live attenuated viral vaccine, presented as a single dose in a sterile and freeze-dried vial, to be reconstituted before subcutaneous injection with diluent (0.4% NaCl₂). The vaccine is presented in a single-dose vial, and diluent is provided in a separate vial. The vaccine contains neither an adjuvant nor a preservative, and after reconstitution, each 0.5 mL dose contains ~5 log₁₀ cell-culture infectious dose 50% (CCID₅₀) per dose of each live, attenuated, dengue virus serotype 1, 2, 3 and 4. The target indication is active immunization for the 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. Dengvaxia (b) (4) DP and diluent are manufactured in different facilities of Sanofi and undergo various quality controls testing including sterility (b) (4) DP and diluent) and endotoxin (DP and diluent) prior to release.


The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released per their product's licensed test method specifications. Therefore, this review will focus on the qualification of sterility and endotoxin methods performed on (b) (4) DP and diluent NaCl₂ of Dengvaxia to determine if they were appropriately qualified to indicate if the matrixes are suitable for these intended test methods.

Review

(b) (4)


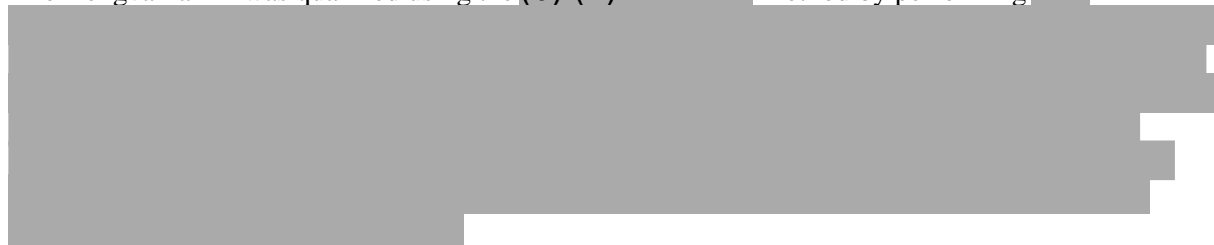


(b) (4)





Sterility Test Qualification for DP

The Dengvaxia DP was qualified using the (b) (4) method by performing (b) (4)







Sterility Test Qualification for Diluent 0.4% NaCl₂

The Dengvaxia diluent 0.4% NaCl₂ was qualified using the (b) (4) method by performing (b) (4)



(b) (4) Bacterial Endotoxin Test ((b) (4)) Qualification for DP

(b) (4)



(b) (4)

(b) (4) Bacterial Endotoxin Test ((b) (4)) Qualification for Diluent 0.4% NaCl₂

(b) (4)

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds Sanofi's Dengvaxia (b) (4), drug product and diluent NaCl₂ matrixes are suitable for testing using their sterility and endotoxin testing methods; these tests were qualified and performed in accordance with (b) (4), respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.