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To: STN: 125682/0

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Subject: Review Memo for Biological License Application for CYD Dengue Vaccine (DENG VAXIA), from Sanofi Pasteur

Recommendation: Approval

Summary of Review:

The BLA, STN125682, was submitted by Sanofi Pasteur to seek approval for its CYD (Chimera Yellow Fever Dengue) Vaccine (DENG VAXIA), a tetravalent, live attenuated viral vaccine, for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 to 17 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

In this memo, the analytical chemistry test methods and their validations, which are proposed to be used for the release testing of DENG VAXIA drug product, were reviewed. The methods include: the appearance of the freeze-dried product, the residual moisture of freeze-dried product, the appearance after dissolution, (b) (4). Based on the information provided in the original submission, as well as in amendments 12 and 36, all the above-mentioned assays have been adequately described and validated for their intended uses; approval is recommended for these assays.

Submitted Information reviewed:

125682

- 1.2 Cover letters
 - Cover Letter STN1 125682 – Seq 0000 – 31Aug2018
- 3.2.P. Drug Product [Product-Dosage Form-Manufacturer]
 - 3.2.P. CYD Gengue Vaccine – UDV – sanofi pasteur
 - 3.2.P.5. Control of Drug Product
 - 3.2.P.5.1. Specification(s)
 - Specification(s)
 - 3.2.P.5.2. Analytical Procedures
 - Analytical Procedures
 - 3.2.P.5.3. Validation of Analytical Procedures
 - Validation of of Analytical Procedures

- 125682/0.12 (Amendment) – Recd 11/20/2018 – DATS# 774244
- 1.11.1 Quality Information Amendment
 - Quality Information Amendment
 - 3.2.P.5.2. Analytical Procedures
 - Q_0143953 – Measure of (b) (4)
 - Q_0143956 - (b) (4)
- 125682/0.16 (Amendment) – Recd 12/13/2018 – DATS# 779116
- 1.11.1 Quality Information Amendment
 - Quality Information Amendment
- 125682/0.23 (Amendment) – Recd 02/15/2019 – DATS# 791526
- 3.2.P.5.4. Batch Analyses
 - Q_0638367 – 323 CYD Dengue Vaccine single-dose (1D) filled product stage – complementary validation of the method for assay of residual moisture using the (b) (4) method
- 125682/0.36 (Amendment) – Recd 03/29/2019 – DATS# 799650
- 3.2.P.5.3. Validation of Analytical Procedures
 - Q_0637840 – Summary of “Specific Protocol for Complementary Validation of the Method for Assay of Residual Moisture in the Dengue Vaccine Q_0637069”

Review Narrative:

CYD Vaccine (DENG VAXIA) is a freeze-dried drug product presented in a glass vials and is reconstituted in 0.4% NaCl solution before being administered by subcutaneous route. One dose of the reconstituted drug product consists of a volume of 0.5 mL.

i) Appearance of the freeze-dried drug product

The DENG VAXIA drug product is a freeze-dried product; its appearance is defined as white homogeneous product freeze-dried with ring-shaped powder residues possible.

Method

The appearance of the DENG VAXIA drug product is determined by visual inspection. A description of the method, including procedure for preparation of the test samples, the execution of the method, and the generation of reportable result, was provided in the BLA. The information provided is adequate and acceptable.

Method Validation


This method is a simple and well-established subjective method and was not validated. This is acceptable because of its simplicity and subjectivity. This method is approvable for the lot release of the DENG VAXIA freeze-dried drug product.

ii) Residual moisture

The water content of DENG VAXIA drug product is determined by (b) (4). The release specification is (b) (4).

Method

(b) (4)



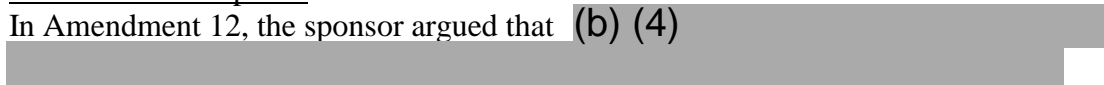
IR question

The following IR was submitted on October 23, 2018 to seek further information from the sponsor:

In section 3.2.P.5.3., you have provided only a brief description on the validation of moisture method for the CYD Dengue freeze-dried product, which only included evaluation of the method's precision. However, the moisture method should be fully validated. Please provide data on the evaluation of accuracy, linearity, range, specificity, robustness, and LOQ for the CYD Dengue freeze-dried product. We recommend that you perform a spike-recovery to evaluate the accuracy and linearity.

Review of the response

In Amendment 12, the sponsor argued that (b) (4)



(b) (4)

The sponsor has not performed specificity evaluation because (b) (4) method is applied specifically for the measurement of water. In addition, since the sponsor has demonstrated acceptable precision, accuracy, linearity, and range of the method, these three validation characteristics together also demonstrate method specificity.

iii) Dissolution time and Appearance after dissolution

The freeze-dried DENG VAXIA drug product is reconstituted in 0.5 mL of 0.4% NaCl solution per dose before being administered. Once the solvent is added, the dissolution time is assessed, and its specification for release is (b) (4). After dissolution, the appearance of the reconstituted drug product is determined by visual inspection as a colorless liquid with possible presence of white or translucent particles.

Method

The assessment of dissolution time and the appearance after dissolution of the DENG VAXIA drug product is determined by visual inspection. A description of the method, including the preparation of the test samples, the execution of the method, and the generation of reportable result, was provided in the BLA. The information provided is adequate and acceptable.

Method Validation

This method is a simple and well-established subjective method and was not validated. This is acceptable because of its simplicity and subjectivity. This method is approvable for the lot release of the DENG VAXIA drug product.

iv) (b) (4) measurement

The (b) (4) value of the reconstituted freeze-dried DENG VAXIA drug product is measured (b) (4) for lot release; its specification is between (b) (4).

Method

In the original application, no information has been provided on the analytical method, and an IR was submitted to seek further information.

Method Validation

This method is an established and simple method, and was not validated. This is acceptable because of its simplicity.

IR question

The following IR was submitted on October 23, 2018 to seek further information from the sponsor:

No information has been provided regarding the methods for (b) (4) for the release testing of the CYD Dengue freeze-dried product. Please provide the relevant SOPs or detailed descriptions on these two methods.

Review of the response

In Amendment 12 submitted on November 20th, 2018, the sponsor responded to the IR by providing English translation of the relevant SOP (Q_0143953 version 6.0). In the SOP, in-depth information has been provided on the preparation of the samples, execution of the method, and generation of the reportable result. The response to the IR is sufficient, and the description on the method is acceptable.

Based on the information from both the original BLA and Amendment 12, the method is approvable for the lot release of the DENG VAXIA drug product.

v) (b) (4)

When the freeze-dried DENG VAXIA drug product is reconstituted for injection, the (b) (4) of the solution is measured by (b) (4) method. The specification for the reconstituted drug product is between (b) (4).

Method

In the original application, no information has been provided on the analytical method, and an IR was submitted to seek further information.

Method Validation

This method is an established method, and can be considered as an instrumental method; the method was not validated. This is acceptable because of its simplicity.

IR question

The following IR was submitted on October 23, 2018 to seek further information from the sponsor:

No information has been provided regarding the methods for (b) (4) for the release testing of the CYD Dengue freeze-dried product. Please provide the relevant SOPs or detailed descriptions on these two methods.

Review of the response

In Amendment 12 submitted on November 20th, 2018, the sponsor responded to the IR by providing English translation of the relevant SOP (Q_0143956 version 9.0). In the SOP, in-depth information has been provided on preparation of the samples, execution of the method, assay validity criteria, and generation of the reportable result. The assay result is valid when the following conditions are met: i) the measured value of the calibration standard is within (b) (4); and ii) the relative standard deviation between the (b) (4) measurements of one sample is (b) (4). The response to the IR is adequate, and the description on the method is acceptable.