

DBSQ/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125777/0

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Alicia Howard, Ph.D.	Lead Reviewer	10/03/2023		Muhammad Shahabuddin, Ph.D.	
Karla Garcia	Reviewer	08/03/2023		Simleen Kaur, M.S.	
Tao Pan Ph.D.	Reviewer	08/01/2023		Kenneth S. Phillips, Ph.D.	

Through Maryna Eichelberger, Ph.D.
Division Director, DBSQ/OCBQ

Applicant: Valneva Austria GmbH

Subject: Analytical Methods used for IXCHIQ (Chikungunya Vaccine, Live-Attenuated) Drug Substance and Drug Product Lot Release Testing

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release testing of IXCHIQ (b) (4) DP and the associated analytic method validations or qualifications, were reviewed:

1. (b) (4) Karla Garcia
2. (b) (4) Karla Garcia
3. Endotoxin (b) (4) DP), Karla Garcia
4. Sterility (DP), Karla Garcia
5. (b) (4), Tao Pan
6. (b) (4), Tao Pan
7. (b) (4), Tao Pan
8. (b) (4) Tao Pan
9. Recombinant Human Albumin (rHA) (b) (4) DP), Tao Pan
10. Sucrose and D-Sorbitol by (b) (4) DP), Tao Pan
11. L-Methionine by (b) (4) DP), Tao Pan
12. Appearance and solubility (DP), Tao Pan
13. Extractable volume (DP), Tao Pan

- 14. Residual moisture (DP), Tao Pan
- 15. (b) (4) [redacted] Alicia Howard
- 16. (b) (4) [redacted] Alicia Howard
- 17. (b) (4) [redacted], Alicia Howard
- 18. Identity (b) (4) DP, Alicia Howard
- 19. Infectious Virus Concentration (b) (4) DP, Alicia Howard

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the IXCHIQ (b) (4) [redacted] drug product were found to be adequate for their intended use.

Documents Reviewed:

Information in sections of the original submission that describe control of DS and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed. Additional information in amendments specified by each reviewer were also reviewed.

Background:

IXCHIQ is a live-attenuated, single dose vaccine intended for active immunization for the prevention of disease caused by Chikungunya (CHIKV) virus in individuals 18 years and older. IXCHIQ is based on the La Reunion strain (LR2006-OPY1) of the (b) (4) [redacted] genotype and attenuated by a deletion of (b) (4) amino acids within the (b) (4) [redacted] part of the non-structural protein 3 (nsP3) of the replicase complex leading to a reduced replication capability of the virus. The IXCHIQ (b) (4) [redacted] harvest concentrate of live-attenuated CHIKV propagated in Vero cells and diluted in formulation buffer; the IXCHIQ DP is lyophilized powder of sterile-filtered formulated DS in a single-use vial, to be reconstituted with 0.5 mL sterile water in a prefilled syringe before injection.

(b) (4) [redacted]

[redacted]

(b) (4)

[redacted]

2 pages determined to be not releasable: (b)(4)

(b) (4)

3. Endotoxin (b) (4) DP)

Introduction

Endotoxin testing for IXCHIQ (b) (4) DP is performed at Valneva (b) (4) (Valneva). Specifications of (b) (4) and (b) (4) DP must be met for release of IXCHIQ.

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Conclusion

The method suitability test was performed and compliant with (b) (4) and the test results indicate there is no product interference from (b) (4) DP test samples, thus indicating the (b) (4) test method is appropriate under the actual conditions of use.

4. Sterility (DP)

Introduction

Sterility testing is performed on DP at (b) (4). Acceptance criteria of 'No Growth Detected' must be met for the lot release of IXCHIQ.

1 page determined to be not releasable: (b)(4)

Conclusion

The method suitability tests were performed and compliant with (b) (4) and the test results indicate there is no product inhibition of microorganism growth, thus indicating the (b) (4) sterility test method is appropriate under the actual conditions of use.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

2 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

9. Recombinant Human Albumin (b) (4) DP

Recombinant human albumin (rHA) is a component of the formulation buffer with a target concentration of 0.1 mg/mL for (b) (4) reconstituted DP; the rHA concentration in (b) (4) reconstituted DP is determined by a (b) (4) method; its release specifications are (b) (4) DP. The method was performed and validated for the release of (b) (4) DP at Valneva (b) (4)

(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

Conclusion:

Based on information provided, the rHA by (b) (4) method has been validated for the release testing of (b) (4) DP.

10. Sucrose and D-Sorbitol (b) (4) DP)

Both sucrose and D-sorbitol are components of the formulation buffer, with respective target concentrations of (b) (4) the concentrations of sucrose and D-sorbitol in (b) (4) reconstituted DP are determined using a (b) (4) method; the release specifications are the (b) (4) DP: (b) (4), respectively. The method was performed and validated for the release of (b) (4) DP at Valneva (b) (4)

(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

Conclusion:

Based on information provided, the sucrose and D-sorbitol by (b) (4) method has been validated for release testing of (b) (4) DP.

11. L-Methionine (b) (4) DP)

L-Methionine is a component of the formulation buffer, with a target concentration of (b) (4); the concentrations of L-Methionine in (b) (4) reconstituted DP are determined using a (b) (4) method; release specifications are the (b) (4) DP: (b) (4). The L-Methionine by (b) (4) assay was performed and validated for the release of (b) (4) DP at Valneva (b) (4)

3 pages determined to be not releasable: (b)(4)

Conclusion:

Based on information provided, the L-Methionine by (b) (4) method has been validated for release testing of (b) (4) DP.

12. Appearance and solubility (DP)

The appearance and solubility of the DP, including both lyophilized and sWFI-reconstituted DP, is determined by visual inspection. The same set of specifications apply to both release and stability of the DP: for lyophilized DP, the appearance is “White to slightly yellowish homogeneous cake with no visible particles or significant cracks”, and the solubility is “Soluble within 1 min upon reconstitution”; for DP after reconstituted in sWFI, the appearance is “Clear colorless to slightly yellowish solution”. The method is performed for the release of DP at Valneva (b) (4)

Method and Method Verification:

No description of the method was provided in the original submission; as a response to Information Request#20 on March 10, 2023, the SOP (VIE-SOP-0387) for the appearance and solubility of the lyophilized DP and the SOP (VIE-SOP-0154) for the appearance of reconstituted DP were submitted in Amendment #26 on April 7, 2023; the latter is the same SOP for the determination of the (b) (4) appearance. In brief, lyophilized DP is first (b) (4)

(b) (4)
The description is acceptable.

The appearance and solubility method is a simple method: in the batch analysis, all (b) (4) lots DP tested were determined to be “White homogeneous cake with no visible particles or significant cracks” and “Soluble within 1 min upon reconstitution” as lyophilized powder, “Clear colourless” after reconstitution in sWFI, and met the release specifications.

Conclusion:

Based on information provided, the appearance and solubility method has been verified for its intended use of release testing of the DP.

13. Extractable Volume (DP)

The extractable volume of the DP (reconstituted in sWFI, 0.5 mL/dose) is determined by (b) (4) method; the specification for release is ≥ 0.5 mL, and it is performed and verified at Valneva (b) (4) for the release of the DP.

Method:

The extractable volume method for the DP is aligned with (b) (4) and (b) (4) but no description of the method has been provided in the original submission; as a response to Information Request #20 on March 10, 2023, the SOP (VIE-SOP-0129) of the test method was

submitted in Amendment #26 on April 7, 2023. In brief, after equilibrated at (b) (4)

[Redacted]

The description is acceptable.

Method Verification:

In the verification, the precision of the method was demonstrated by (b) (4)

[Redacted]

Conclusion:

Based on information provided, the extractable volume method has been verified for its intended use of release testing of the DP.

14. Residual Moisture (DP)

The residual moisture of the DP is determined with a (b) (4) method; its specifications are (b) (4)

Method:

The residual moisture method for DP is based on (b) (4)

[Redacted]

The description on the analytical method provided is sufficient.

(b) (4)

[Redacted]

[Redacted]

(b) (4)

[Redacted text block]

Conclusion:

Based on information provided, the residual moisture by (b) (4) method has been validated for the release and stability testing of lyophilized DP.

9 pages determined to be not releasable: (b)(4)

(b) (4)

18. Identity (b) (4) DP

Introduction

The (b) (4) method is outlined in document VIE-SOP-0475[03]. This is a release test for the (b) (4) the DP. The release specification for the (b) (4) DP is a positive result. The test for (b) (4) and the test for DP is performed at Valneva (b) (4) Method validation for (b) (4) DP are reviewed in this section.

Method

The purpose of this method is to determine identity of the CHIKV (b) (4) DP samples prior to release. The assay is performed in (b) (4)

(b) (4)

5 pages determined to be not releasable: (b)(4)

(b) (4)

19. Infectious Virus Concentration (b) (4) DP)

Introduction

The purpose of the TCID₅₀ method is to measure the infectious virus content of (b) (4) DP. The Chikungunya virus infectious titer is measured in the (b) (4)

The test is performed at the Valneva (b) (4)

(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)



Conclusion

The Determination of Infectious Virus Concentration by TCID₅₀ method was appropriately validated for its intended purpose at Valneva (b) (4) and is suitable for the determination of infectious virus content in IXCHIQ (b) (4) samples; the firm has committed (Amendment #79) to submit additional data demonstrating the suitability of the assay for measuring DP throughout the range. Despite not having these data, in my opinion, the assay is suitable for lot release testing of DP because the matrix is similar to that of the (b) (4) and lower limit studies with the (b) (4) support linearity and repeatability throughout the DP range.