



**DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO**

**To:** STN 125820/0

**From:** Hsiaoling Wang, Ph.D., CMC Reviewer, CBER/OCBQ/DBSQC/LAC

**Through:** Kenneth Phillips, Ph.D., LAC Chief, CBER/OCBQ/DBSQC/LAC  
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**Product:** Recombinant Chikungunya Vaccine

**Applicant:** Bavarian Nordic

**Subject:** Review of analytical procedures for the lot release of Recombinant Chikungunya Vaccine (b) (4) and drug product

**Recommendation:** Approval

**Review Summary:**

The following analytical methods used for lot release of the recombinant Chikungunya vaccine and the associated validations or qualifications, were reviewed:

1. (b) (4) by (b) (4)
2. Total Protein Concentration by (b) (4) DP)
3. (b) (4) by (b) (4)
4. Aluminum content (DP)
5. Appearance (b) (4) DP)
6. pH (b) (4) DP)
7. (b) (4)
8. Subvisible Particulates (DP)
9. Container Content (DP)

**Conclusion:** The analytical methods and their qualifications reviewed for the recombinant Chikungunya vaccine (b) (4) drug product (DP) were found to be adequate for their intended use.

**Documents Reviewed**

Rolling submission, started on April 26, 2024:

- Cover letter
- Form 356h
- Sections describing control of (b) (4) DP (3.2.P.5), including descriptions of (b) (4) DP specifications, analytical procedures of (b) (4) DP, qualifications of these analytical procedures, and (b) (4) DP batch analyses.

Amendment 25, dated October 4, 2024

- Response to FDA IR #20 dated 20-Sep-2024
- Work Instruction BN0082039: (b) (4)
- Work Instruction BN0082167: Appearance of liquids
- Work Instruction BN0095630: Determination of Total Protein Concentration using (b) (4)
- Validation report BN0104185: Purity and protein composition of CHIKV VLP (b) (4) by (b) (4)
- Verification report BN0113708: CHIKV VLP (b) (4) Verification Report
- Updated verification report BN0194487: (b) (4)  
(b) (4)

Amendment 46, dated November 29, 2024

- Response to FDA CMC IR #36 dated 18-Nov-2024

Amendment 49, dated December 13, 2024

- Response to FDA CMC IR #43 dated 05-Dec-2024

Amendment 58, dated January 7, 2024

- Response to FDA CMC IR #43 dated 05-Dec-2024
- BN0204776: Method validation report of (b) (4)  
(b) (4)

Amendment 62, dated January 22, 2025

- Response to FDA CMC IR #43 dated 13-Jan-2025
- Updated BN0204776: Method validation report of (b) (4)  
(b) (4)

## Background


On April 26, 2024, Bavarian Nordic started to submit a rolling original Biologics License Application (BLA), STN125820, for approval of its recombinant Chikungunya vaccine. It is indicated to prevent disease caused by chikungunya virus infection in individuals 12 years of age and older through intramuscular administration.

The recombinant Chikungunya vaccine DS is composed of (b) (4)

The recombinant Chikungunya vaccine DP is a sterile aqueous buffered suspension comprised of 40 µg CHIKV VLP adsorbed on aluminum hydroxide adjuvant (300 µg aluminum) and stabilized with the same formulation buffer as that of DS. It is provided in a single dose 1-mL pre-filled glass syringe (0.8 mL deliverable dose volume) and is stored at 2-8°C.

#### **Review Narrative**

(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

## 2. Total Protein Concentration by (b) (4) DP

The total protein concentration specification is (b) (4). The total protein concentration specifications are (b) (4) for (b) (4) and (b) (4) for DP.

### Method (WI041192)

The method description is provided in 3.2.S.4.2 Analytical procedure [Chikungunya Virus VLP, Bavarian Nordic (b) (4) -3.4 Protein Concentration and 3.2.P.5.2 Control of Drug Product, analytical Procedures [CHIKV VLP DP, Suspension for injection] – 1.5. Total Protein Concentration.

The protein concentration is determined by a (b) (4)

(b) (4)

(b) (4)

The firm did not state the acceptance criterion for assay RSD. An IR was sent to the firm in IR #20 to request the RSD acceptance criterion of (b) (4) DP sample from its (b) (4) measurements. The firm responded that the acceptance criterion is (b) (4) in amendment 25. The updated work instruction BN0095630 was also provided in amendment 25. The response is acceptable.

### Method Validation

The method was validated at (b) (4) and documented in reports BN0096879 (according to PRO046400) for (b) (4) and BN0096870 (according to PRO046406) for DP. As a quantitative assay, it was validated for characteristics of specificity, precision, accuracy, linearity, range, and robustness.

The method was validated using (b) (4) and (b) (4) DP lot (b) (4).  
(b) (4) Results are summarized in the table below.

Validation Characteristic	Acceptance Criteria	Results
(b)	(4)	

(b) (4)

During the repeatability study, the (b) (4)

The run was repeated, and the results were acceptable.

#### Method Transfer

BDP Chikungunya Virus Virus-like Particles (CHIKV VLP) is manufactured at (b) (4). The BDP will be transferred to (b) (4) for further manufacturing and filled into 1 mL syringes. The (b) (4) site will perform the total protein concentration by (b) (4) for final drug product release. The method transfer of (b) (4) from (b) (4) to (b) (4) is reported in BN0112091. The test method (b) (4) used by (b) (4) is equivalent to the SOP (b) (4) used by (b) (4).

(b) (4) was used for the method transfer. (b) (4) trained analyst each from the receiving and transferring performed the repeatability and reproducibility studies. There was total (b) (4) independent measurements and the mean protein results were (b) (4) from (b) (4) and (b) (4) from (b) (4). Both met the specification of (b) (4) with (b) (4) of (b) (4). The RSD of repeatability (b) (4) from (b) (4) was (b) (4) which met the acceptance criterion of (b) (4). The RSD of reproducibility by (b) (4) was (b) (4) which met the acceptance criterion of (b) (4).

#### Conclusion

Based on the information provided in the original BLA and Amendment 25, the method has been validated and transferred successfully for release testing.

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(b) (4)

#### **4. Aluminum content (DP)**

Aluminum hydroxide serves as adjuvant and stabilizer of the product. The aluminum content specification is (b) (4) for (b) (4) DP.

##### Method

The method description is provided in 3.2.P.5.2 Control of Drug Product, analytical Procedure [CHIKV VLP DP, Suspension for injection]- 1.3. Aluminum Content.

Aluminum concentration in (b) (4) DP is quantified by (b) (4)  
(b) (4)

(b) (4)

(b) (4)

#### Method Validation

The method was validated at (b) (4) site and documented in reports BN0097404 (according to PRO047084). As a quantitative assay, it was validated for characteristics of specificity, accuracy, precision, linearity, range, and robustness.

(b) (4) were used for method validation. Results are summarized in the table below.

Validation Characteristic	Acceptance Criteria	Results
(b) (4)	(b) (4)	

(b) (4)

#### Method Transfer

The (b) (4) site will perform the aluminum content for final drug product release. The method transfer of this assay from (b) (4) to (b) (4) is reported in BN0112093. The test method (b) (4) used by (b) (4) is equivalent to the (b) (4) used by (b) (4)

(b) (4) was used for the method transfer. (b) (4) trained analyst each from the receiving and transferring labs performed the repeatability and reproducibility studies. There were total of (b) (4) measurements and the mean aluminum results were (b) (4) from (b) (4) and (b) (4) from (b) (4). Both met the specification of (b) (4) with (b) (4) of (b) (4). The RSD of repeatability (b) (4) from (b) (4) was (b) (4) which met the acceptance criterion of (b) (4). The RSD of reproducibility by (b) (4) labs was (b) (4) was (b) (4) which met the acceptance criterion of (b) (4)

#### Conclusion

Based on the information provided in the original BLA and amendment 25, the method has been validated and transferred for its intended use.

## 5. Appearance (b) (4) DP

(b) (4) (b) (4) The appearance specifications are (b) (4) (b) (4) white, cloudy liquid free of visible extraneous particles for DP.

### Method

The analytical procedure for (b) (4) DP appearance test (BN0082167) was provided in Amendment 25 upon FDA's request.

(b) (4)

### Method Verification

No method verification report was submitted from the (b) (4) lab. The firms stated that analysts were trained and qualified to perform the appearance by internal procedure (b) (4) in 3.2.S.4.3

Validation of Analytical Procedures [Chikungunya Virus VLP, Bavarian Nordic (b) (4) (b) (4) The firm also stated that analysts are trained and qualified to perform the (b) (4) DP appearance test against in-house control solutions according to the (b) (4) DP specifications in 3.2.P.5.3 Control of Drug Product, Validation of Analytical Procedures [CHIKV VLP DP, Suspension for injection]. In 3.2.S.4.4 Batch Analyses, there are (b) (4) phases 1 and (b) (4) lots, (b) (4) phase 3 (b) (4) lots, (b) (4) engineering (b) (4) lots, (b) (4) process performance qualification (PPQ) (b) (4) lots and (b) (4) GMP (b) (4) lots. In 3.2.P.5.4 Batch Analyses, there are (b) (4) phase (b) (4) lots, (b) (4) engineering (b) (4) lots, PPQ (b) (4) lots and 2 GMP (b) (4) lots. There are also (b) (4) phases 1 and (b) (4) DP lots, phase (b) (4) DP lots, (b) (4) engineering DP lot, (b) (4) PPQ DP lots and (b) (4) phase (b) (4) DP lots. Their appearance results from (b) (4) lab were all in compliance with the proposed (b) (4) (b) (4) (b) (4) DP specifications.

The (b) (4) site provided visual inspection verification report BN0113708 in Amendment 25 upon this reviewer's request. The test method (b) (4) used by (b) (4) is equivalent to that of (b) (4) was tested by (b) (4) trained analyst and (b) (4) appearance analyses were made. All results were in compliance with the DP specifications.

### Conclusion

Based on the information provided in the original BLA and Amendment 25, this (b) (4) method was adequately verified for its intended purpose.

## 6. pH (b) (4) DP)

The pH specifications are (b) (4) for (b) (4) DP.

### Method

The pH determination is according to (b) (4) and (b) (4) for (b) (4) (b) (4) DP samples. The (b) (4) method uses (b) (4)

The pH is measured at (b) (4)

### Method Verification

Suitability of the pH test for (b) (4) (b) (4) was described in document BN0097752 from (b) (4) site. The verification is also applicable for DP because DP is the (b) (4) filled into a glass syringe. The precision study was conducted. The repeatability of (b) (4) independent determinations from (b) (4) analyst had RSD of (b) (4) for (b) (4) and (b) (4) for (b) (4) which met the acceptance criterion of (b) (4) (b) (4). The (b) (4) precision of total (b) (4) determinations by (b) (4) analysts on (b) (4) occasions had RSDs of (b) (4) for (b) (4) which met the acceptance criterion of (b) (4) pH results were (b) (4) for (b) (4) which were within the specification of (b) (4).

The (b) (4) site provided a pH verification report for DP in document BN0113708. The test method (b) (4) used by (b) (4) is equivalent to that of (b) (4) (b) (4) determinations were made for (b) (4) pH results were (b) (4) which were consistent and met the DP specification.

### Conclusion

Based on the information provided in the original BLA, this (b) (4) method was adequately verified for its intended purpose.

(b) (4)

(b) (4)

#### 8. Subvisible Particulates (DP)

The subvisible particles specifications are (b) (4) for particles (b) (4) and (b) (4) for particles (b) (4) for DP.

##### Method

The test is performed according to (b) (4) and (b) (4). The analysis is based on (b) (4).

The acceptance criteria of system suitability (b) (4).

The system suitability standard and acceptance criteria were provided in Amendment 25 upon this reviewer's request. Section 3.2.P.5.2 Control of Drug Product, Analytical Procedures was updated to include this critical information.

##### Method Verification

Suitability of the subvisible particulate matter test was provided in document BN0193875 from the only testing site (b) (4). (b) (4) was measured in (b) (4). The results were (b) (4) per container for particle (b) (4) and (b) (4) per container for particle (b) (4) which met the proposed specifications of (b) (4) per container for particle (b) (4) and (b) (4) per container for particle (b) (4).

Method verification of the sub-visible particulates for DP was provided in document BN00113685 from the (b) (4) which performed the sub-visible particles test for the phase 3 clinical trial DP samples. The test method (b) (4) used by (b) (4) lab is also in accordance with (b) (4) and (b) (4) syringes of a DP lot (b) (4) was (b) (4) as a representative sample for the verification. The results were (b) (4) per container for particle (b) (4) and (b) (4) per container for particle (b) (4) which met the proposed specifications.

#### Conclusion

Based on the information provided in the original BLA and amendment 25, this (b) (4) method is verified for its intended use.

### **9. Container Content (DP)**

The container content specification is (b) (4) 0.8 mL for DP.

#### Method

The container content is determined in accordance with (b) (4) and (b) (4) (b) (4) for DP. (b) (4) DP syringes are (b) (4)

The assay acceptance criterion is (b) (4) (b) (4) In the (b) (4) the (b) (4) is (b) (4) obtained from the historical determinations of the mean of the (b) (4) of (b) (4) mL DP solutions.

#### Method Verification

Suitability of the container content test for DP from the (b) (4) was described in document BN0109698. (b) (4) was used as a representative material for the evaluation. (b) (4) analysts performed the test in total of (b) (4) runs in different days. The container volumes were all (b) (4) which met the proposed specification of (b) (4) 0.8 mL.

Verification of the container content test for DP from the (b) (4) was provided in document BN00113707. The test method (b) (4) used by the (b) (4) lab is equivalent to that of the (b) (4) lab. (b) (4) was used as a representative sample for the evaluation. The container volumes from (b) (4) DP syringes were all (b) (4) mL, which met the proposed specification.

#### Conclusion

Based on the information provided in the original BLA, this (b) (4) method is verified for its intended use.