

### Chemistry, Manufacturing, and Controls Statistical Review

Application Type	Original BLA
STN	125820/0
Applicant	Bavarian Nordic A/S
Trade Name	Chikungunya Vaccine, Recombinant (VIMKUNYA)
Pharmacologic Class	Vaccine
Indication	To prevent disease caused by chikungunya virus infection in individuals 12 years of age and older
Review Priority	Priority
CBER Received Date	06/17/2024
Action Due Date	02/15/2025
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## 1. EXECUTIVE SUMMARY

In this original BLA, Bavarian Nordic A/S (BN) seeks approval for their chikungunya vaccine, VIMKUNYA. This review focuses on the validation of the (b) (4) assays and justification of specification for drug substance (DS), drug product (DP), bulk drug product (BDP), and some excipients. The shelf-life for DP, BDP, and DS was justified based on real-time stability data but not based on statistical analyses. Therefore, this memo does not review the stability or shelf-life setting.

BN provided the validation reports for several (b) (4) quantitative assays used to measure quality attributes for DS, DP, BDP, and excipients. While not all validation study designs and analyses were ideal, the results support the conclusion that the assays have adequate performance over an appropriate range for their respective quality attributes. Most of the validations were performed at the routine testing lab. For assays validated at a different lab than the routine testing lab, BN provided results from transfer studies to support the change in testing lab. While the design and analyses of the transfer studies were not ideal, supplementary analyses suggest that the assays have adequate performance at the receiving labs.

BN also re-examined their DS, BDP, and DP specifications, based on scientific, clinical, and product knowledge, supplemented by historical data from clinical, engineering, process performance qualification, and Good Manufacturing Practices (GMP) batches. Most specification limits were maintained based on development specifications, and those that were changed were justified based primarily on scientific concerns.

Overall, I recommend approval of this original BLA.

## 2. REGULATORY BACKGROUND AND SOURCE OF INFORMATION

In this original BLA, BN seeks approval for their chikungunya vaccine, VIMKUNYA. VIMKUNYA includes an aluminum hydroxide gel (b) (4) adjuvant and is formulated as a suspension in water for injection (WFI). This review focuses on the validation and transfer studies for (b) (4) assays and justification of specification for DS, DP, BDP, and certain excipients. The shelf-life for DP, BDP, and DS was justified based on real-time stability data but not based on statistical analyses. Therefore, I do not review the stability or shelf-life setting.

This review refers to the files submitted to Module 3 of BLA 125820/0.2, as well as the responses (Module 1.11.1) to the information requests:

- IR #19 sent on 19 September 2024 (BLA 125820/0.25),
- IR #20 sent on 20 September 2024 (BLA 125820/0.25),
- IR #36 sent on 18 November 2024 (BLA 125820/0.46),

- IR #43 sent on 5 December 2024 (BLA 125820/0.49),
- IR #49 sent on 18 December 2024 (BLA 125820/0.58),
- IR #50 sent on 20 December 2024 (BLA 125820/0.58),
- IR #54 sent on 13 January 2025 (BLA 125820/0.62).

All the responses to the information requests were adequate.

### 3. DISCUSSION OF PROTOCOLS, STUDIES OR ANALYSES, AND RESULTS

#### 3.1 Assay Validation and Transfer Studies

BN validated different quality attributes using different study designs for the DS, DP/BDP, and excipients (b) (4) WFI). Table 1 summarizes the quantitative, (b) (4) (b) (4) assay validation and comparability studies that I reviewed. In some cases, the assay validation was performed at a different lab than the release lab, in which case, a transfer study was performed.

(b) (4) is the (b) (4) measured by (b) (4), and (b) (4) (b) (4) is calculated from the (b) (4) and the (b) (4) (b) (4) The in (b) (4) is calculated as the (b) (4) (b) (4) Therefore, BN did not provide separate validation results for the potency.

**Table 1.** Validation Studies by Quality Attribute

Quality Attribute	Assay	Validation Lab(s)	Release Lab	Validation Test Material	Release Test Material
(b) (4)	(b) (4)	(b) (4)	(b) (4)	DP/(b) (4)	DP/(b) (4)
(b) (4)	(b) (4)			DP	DP
Total Protein Concentration	(b) (4)			DP/(b) (4)	DP/(b) (4)
Aluminum Content	(b) (4)			DP/(b) (4)	DP/(b) (4)
Particle Size	(b) (4)			(b) (4)	(b) (4)
Purity	(b) (4)			(b) (4)	(b) (4)
Purity	(b) (4)			(b) (4)	(b) (4)
Residual Host Cell Protein	(b) (4)			(b) (4)	(b) (4)
(b) (4)	(b) (4)			(b) (4)	(b) (4)
(b) (4)	(b) (4)			(b) (4)	(b) (4)

\*Transfer study performed

(b) (4)

Source: Module 3, BLA 125820/0.2

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### 3.1.3 Total Protein Concentration

#### 3.1.3.1 Validation Study

For total protein concentration, BN used the same study design for (b) (4) /DP.

(b) (4)

**Reviewer's Comment:** *As noted previously, accuracy is usually assessed* (b) (4)

(b) (4)

(b) (4)

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(b) (4)

**Reviewer's Comment:**

*I reproduced the total protein concentration precision results. In the original reports, the precision results were (b) (4). This is not appropriate, as (b) (4) may hide meaningful differences in precision across the assay's range. CBER sent an IR #50 on December 20, 2024, to request the (b) (4) (b) (4) to assess precision for (b) (4) DP of total protein concentration. BN responded and provided the requested (b) (4) (Table 10). Results met the acceptance criterion. During routine testing, (b) (4) and DP samples are (b) (4)*

*his assay is validated over an acceptable range.*

**3.1.3.2 Transfer Study**

(b) (4) will be transferred from (b) (4) to (b) (4) for further processing during commercial manufacturing. Therefore, (b) (4) will perform the (b) (4) during routine testing for (b) (4) DP.

(b) (4)

(b) (4)



(b) (4)

*While the transfer study design is not ideal, none of the results suggest that the new site is unacceptably imprecise or differs substantially from the current site.*

#### 3.1.4 Aluminum Content

(b) (4) DP (b) (4) are tested for aluminum content. Therefore, BN separately validated the assay for testing (b) (4)/DP (b) (4)

##### 3.1.4.1 Drug Product Validation Study

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)


**Reviewer's Comment:** *BN's precision results were* (b) (4)

*Results met the acceptance criteria.*

Based on these results, BN considers the assay validated over a range of (b) (4)  
(b) (4) which covers the specification (b) (4)

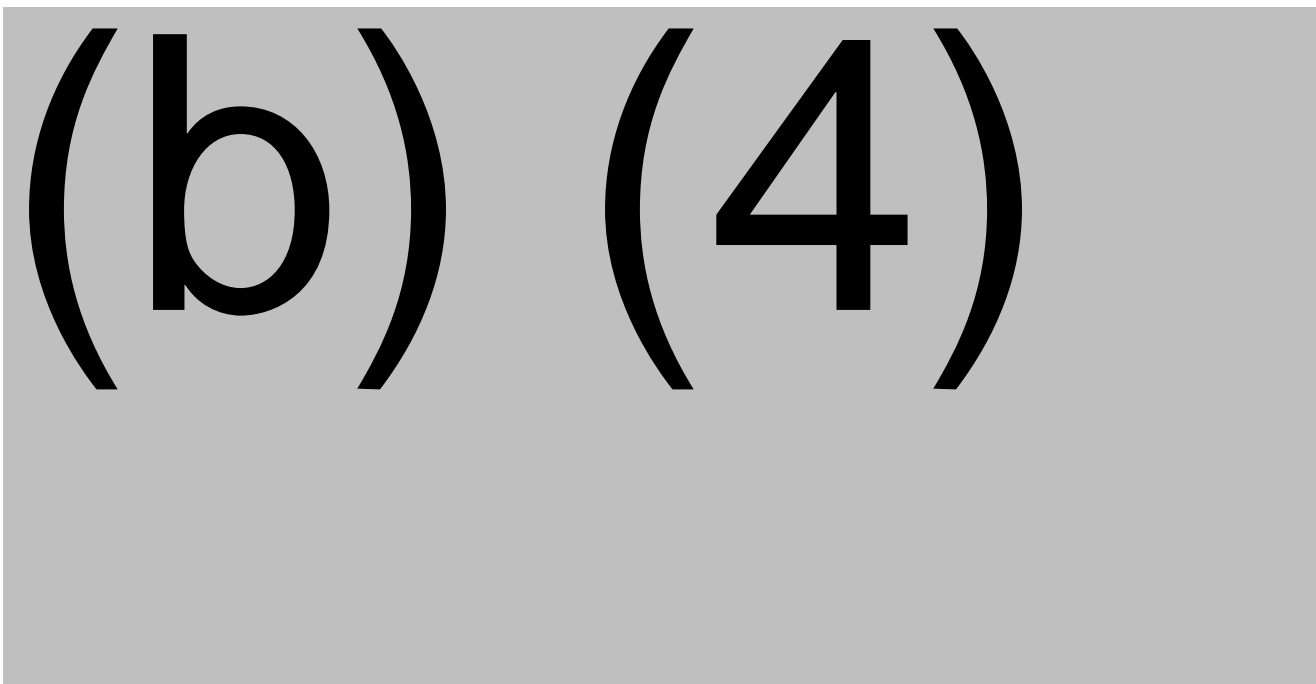
#### 3.1.4.2 Drug Product Comparability Study

Routine testing for aluminum content in (b) (4)/DP will be performed at (b) (4) so BN completed a transfer study. To assess comparability between (b) (4)



(b) (4)

(b) (4)



(b) (4)

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(b) (4)

### 3.2 Justification of Specifications

BN used historical data from Phase 3 clinical batches, engineering batches representative of the commercial manufacturing process, process performance qualification (PPQ) batches, and GMP batches manufactured post-PPQ to justify the specification. Table 23 shows a summary of the historical data available to re-evaluate the DP, (b) (4) specifications.

(b) (4)

Tables 24 and 25 show the current (development) and proposed release and stability specification limits. BN re-assessed these limits based on a combination of clinical, scientific, and product knowledge; clinical and toxicological data as relevant, and in some cases, statistical analysis (b) (4)

The statistical analyses were based on a mixed effects model with a random effect for batch to account for the repeated measurements.

(b) (4)

Many of the quality attributes had tolerance intervals that were similar to or more permissive than the existing specifications. Therefore, most of the specification limits remain unchanged from the development specifications. Of those specification limits that changed, those for (b) (4) and total protein concentration are stricter.

**Reviewer's Comment:** *In general, BN did provide a justification for their normal distribution-based tolerance intervals (TI), although many variables that are likely to be (b) (4) distributed were analyzed on the (b) (4) (b) (4). However, in general, the appropriateness of the TI will depend on how well the normal distribution fits the data.*

*The total protein specification was (b) (4) based on product knowledge.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**Reviewer's Comment:** BN's proposed changes to the (b) (4) potency specification limits are based on the mean of the historical data and the existing limits, with a justification based on (b) (4) data. Therefore, I did not review the TIs for the (b) (4) potency.

(b) (4)

*The product reviewer considers this acceptable; therefore, no questions will be raised.*

#### 4 CONCLUSIONS

BN provided the validation reports of several (b) (4) quantitative assays used to measure quality attributes for (b) (4) DP, (b) (4) and excipients. While the validation study designs and analyses were not all ideal, the results support the conclusion that the assays have adequate performance over an appropriate range for their respective quality attributes. Most of the validations were performed at the routine testing lab. For assays validated at a different lab than the routine testing lab, BN provided results from transfer studies to support the change in testing lab. Overall, while the design and analyses of the transfer studies were not ideal, my supplementary analyses suggest that the assays have adequate performance at the receiving labs.

BN also re-examined their (b) (4) DP specifications, based on scientific, clinical, and product knowledge, supplemented by historical data from clinical, engineering, process performance qualification, and GMP batches. Most specification limits were

maintained based on development specifications, and those that were changed were justified based primarily on scientific concerns.

Overall, I recommend approval of this original BLA.