

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125820/0

**Established Name: Chikungunya Vaccine, Recombinant (CHIKV)
Proprietary Name: VIMKUNYA**

Wei Wang, Ph.D., OCBQ/DMPQ/MRB3

1. BLA#: STN 125820/0**2. APPLICANT NAME AND LICENSE NUMBER:** Bavarian Nordic Inc., US license Number: 2096**3. PRODUCT NAME/PRODUCT TYPE**

- Established Name: Chikungunya Vaccine, Recombinant (CHIKV)
- Proprietary Name: VIMKUNYA

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- Pharmacological category: The recombinant chikungunya virus vaccine (CHIKV) is comprised of three recombinant chikungunya virus structural proteins (Capsid, C, Envelope 1, E1, and Envelope 2, E2) derived from chikungunya virus Senegal strain 37997, which self-assemble to form a spherical virus-like particles.
- Dosage form: Suspension for injection.
- Strength/Potency: 40 µg CHIKV.
- Route of administration: Intramuscular.
- Indication(s): Prevention of disease caused by chikungunya virus infection in individuals 12 years of age and older.

5. MAJOR MILESTONES

Application Receipt Date	June 17, 2024 (Module 3)
Filing Date	August 16, 2024
Pre-License Inspections (PLI)	<ul style="list-style-type: none">A PLI of (b) (4) facility was performed (b) (4)A PLI of (b) (4) (b) (4) was performed (b) (4)A PLI of (b) (4) was performed (b) (4)A PLI of (b) (4) was performed (b) (4)
Midcycle Date	October 1, 2024 (internal) October 17, 2024 (with applicant)
Late-cycle Date	November 19, 2024 (internal) December 1, 2024 (with applicant)
PDUFA Action Due Date	February 15, 2025

6. CMC/QUALITY REVIEW TEAM

Reviewer Name / Initials / Branch	Section / Subject Matter
Wei Wang, Ph.D., OCBQ/DMPQ/MRB3	<ul style="list-style-type: none">Module 1: Administration InformationModule 2: Common Technical Document Summaries

	<ul style="list-style-type: none"> Module 3: <ul style="list-style-type: none"> 3.2.S Drug Substance 3.2.P Drug Product 3.2.A.1 Facilities and Equipment
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7. INTER-CENTER CONSULTS REQUESTED

Reviewer Name / Affiliation	Section / Topic	Agree with consult recommendation (Yes/No)
None	None	N/A

8. SUBMISSION(S) REVIEWED

Receipt Date	Submission Number	Status / Comment
June 17, 2024	STN 125820/0.2	Modules 1, 2 and 3 reviewed
August 16, 2024	STN 125820/0.11	Module 1, Dates of pre-license inspection (PLI) of (b) (4) (b) (4) and (b) (4)
November 22, 2024	STN 125820/0.42	Module 1, Response to IR #38 (the initial (b) (4) 483 Responses)
December 13, 2024	STN 125820/0.49	Section 3.2.A.1 Response to IR #38 (updated APS information)

9. Referenced REGULATORY SUBMISSIONS

Review Comments: The applicant provided a letter of authorization (LOA) in Section 1.4.2 of STN 125820/0.2 (CBER received on June 17, 2024) for each of referenced submissions listed in table below.

Submission Type & No.	Holder	Referenced Item	Status / Comment
(b) (4)			

(b) (4)

10. REVIEWER SUMMARY AND RECOMMENDATION
A. EXECUTIVE SUMMARY

Bavarian Nordic submitted this BLA, STN 125820/0, for the manufacture of VIMKUNYA (Chikungunya Vaccine, Recombinant, abbreviated as CHIKV) for the prevention of disease caused by chikungunya virus infection in individuals 12 years of age and older.

The recombinant CHIKV vaccine is a non-replicating enveloped virus like particle comprising three structural proteins (including a capsid/core protein, C, and two envelope proteins, E1 and E2) derived from chikungunya virus Senegal strain 37997. CHIKV is produced by recombinant DNA technology using HEK293 cells (also known as (b) (4) in this submission) as host cells.

The CHIKV drug substance (DS) and formulated bulk drug product (BDP) are manufactured in the Bavarian Nordic (b) (4) facility in (b) (4). The (b) (4) is shipped to (b) (4) facility in (b) (4) and is filled to manufacture drug product (DP) in prefilled syringes (PFS). The DP PFS is labelled and packaged at (b) (4) facility in (b) (4). To support the review of this BLA, CBER conducted (b) (4) pre-license inspections (PLI), including (b) (4).

All 483 issues were resolved, and the inspection was classified as VAI. CBER waived the PLI of (b) (4).

This review memo covers Chemistry, Manufacturing and Controls (CMC), with a focus on the microbial controls, facility, major equipment, cleaning, environmental monitoring (EM) and cross-contamination controls.

B. RECOMMENDATION

I. APPROVAL

DMPQ recommends approval of this BLA, STN 125820/0, to manufacture CHIKV drug substance (DS) and formulated bulk drug product (BDP) at Bavarian Nordic (b) (4) (b) (4) to fill CHIKV DP into syringes at (b) (4) (b) (4) and to label and package the finished DP (FDP) at (b) (4).

The applicant committed to submit a final report of FDP transport validation study as a PMC submission by June 30, 2025 (PMC#3), and a final report of DP transportation validation using the DP PPQ lots as a PMC submission by February 28, 2026 (PMC#4).

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer Name / Title / Branch	Concurrence	Signature and Date
Wei Wang, Ph.D. CMC and Facility Reviewer OCBQ/DMPQ/MRB3	Concur	
CDR Donald Ertel Branch Chief OCBQ/DMPQ/MRB3	Concur	
Carolyn Renshaw Division Director OCBQ/DMPQ	Concur	

Table of Contents

3.2.S DRUG SUBSTANCE	3
3.2.S.1 General Information	3
3.2.S.2 Manufacture	3
3.2.S.2.1 Manufacturer(s)	3
3.2.S.2.2 Description of Manufacturing Process	5
3.2.S.2.3 Control of Materials	7
3.2.S.2.4 Controls of Critical Steps and Intermediates	7
3.2.S.2.5 Process Validation and/or Evaluation	7
3.2.S.2.6 Manufacturing Process Development	11
3.2.S.3 Characterization	11
3.2.S.4 Control of Drug Substance	12
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)	12
3.2.S.4.4 Batch Analyses	12
3.2.S.6 Container Closure System (CCS)	12
3.2.S.7 Stability	12
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data	12
3.2.P DRUG PRODUCT	13
3.2.P.1 Description and Composition of the Drug Product	13
3.2.P.2 Pharmaceutical Development	13
3.2.P.2.5 Microbiological Attributes	13
3.2.P.3 Manufacture	14
3.2.P.3.1 Manufacturer(s)	14
3.2.P.3.3 Description of Manufacturing Process	16
3.2.P.3.4 Controls of Critical Steps and Intermediates	20
3.2.P.3.5 Process Validation and/or Evaluation	20
3.2.P.5 Control of Drug Product	26
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)	26
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	26
3.2.P.5.4 Batch Analyses	27
3.2.P.7 Container Closure System (CCS)	27
3.2.P.8 Stability	28
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	28
3.2.A APPENDICES	29
3.2.A.1 Facilities and Equipment (b) (4) – Manufacturing DS and BDP)	29
Overview of (b) (4) Facility and Manufacturing Areas	29
HVAC System and Environmental Monitoring (EM)	30
Utilities	31
Major Equipment and Equipment Cleaning	32
Autoclave Validation	34
(b) (4) Validation	35
Aseptic Process Simulation (APS) Studies	35
3.2.A.1 Facilities and Equipment (b) (4) – Manufacturing DP in PFS)	37
Overview of (b) (4) CHIKV Manufacturing Facility and Manufacturing Areas	37
HVAC System and EM Program in (b) (4) Facility	38

Major Equipment Validations	38
APS by MF (b) (4)	41
3.2.A.1 Facilities and Equipment (b) (4) Labeling and Packaging).....	43
3.2.R Regional Information (USA).....	44
Combination Products	44
Purchasing Controls	44
Corrective and Preventive Action (CAPA)	44
Risk Analysis	45

Module 3

3.2.S DRUG SUBSTANCE

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The applicant indicated the following:

- The CHIKV vaccine is a sterile aluminum hydroxide-adjuvanted DP, filled as a single dose of 0.8 mL into 1-mL pre-filled syringe (PFS), and administered by intramuscular (IM) injection.
- The CHIKV bulk DP (BDP) is produced by (b) (4)
(b) (4)
- The (b) (4) is then filled into 1 mL PFS. The filled syringe is sealed with a chlorobutyl rubber plunger stopper to create the CHIKV DP.
- The unlabeled CHIKV DP in PFS is then individually labeled, assembled by the addition of a polypropylene finger flange and plunger rod to create the finished DP (FDP) which is individually packaged in a carton. The CHIKV vaccine PFS is classified as a single-entity drug/device combination product.

3.2.P.2 Pharmaceutical Development

3.2.P.2.5 Microbiological Attributes

Microbiological Attributes

The applicant stated the following microbiological controls and testing:

(b) (4)

- The CHIKV DP is manufactured aseptically by aseptic connection of the BDP (b) (4) to the syringe filling line located inside a Grade (b) (4) and filling the BDP into syringes and then stoppering with syringe plunger. The DP is stored at 2-8°C and shipped (at 2 – 8°C) to a contractor FDP manufacturing facility.
 - Sterility and endotoxin are tested for the release of CHIKV DP.
- The CHIKV FDP manufacturing processing steps include the addition of plunger rod, syringe label, finger flange, and placement into a tray and carton. The FDP is stored at 2-8°C.
 - Sterility and endotoxin are tested for the release of CHIKV FDP.

Container Closure Integrity Testing (CCIT)

The applicant indicated that CCIT (using a (b) (4) method using a positive defect (b) (4) (b) (4) reviewed in Section 3.2.P.5.2) is performed for the CHIKV DP (PFS) stability in lieu of sterility testing during stability studies.

Overall Reviewer's Assessment of Section 3.2.P.2:

- The information under the DMPQ purview appeared acceptable as submitted.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

In Section 3.2.P.3.1 of STN 125820/0.2 (CBER received on 6/17/2024), the applicant provided information of manufacturers and testing sites (summarized in table below) for CHIKV BDP, DP, and FDP.

Table 4. Facilities for Manufacturing and Testing of CHIKV BDP, DP, and FDP

Facility and Identification	Responsibilities
Bavarian Nordic (b) (4) (b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none"> • Manufacture of BDP • All in-process testing (IPT) • Release of BDP, DP and FDP • DS release testing (e.g., (b) (4) and stability testing • Storage and stability testing of HEK 293 (also referred as (b) (4) cells) master cell bank (MCB) and working cell bank (WCB) • Storage of (b) (4) MCB and WCB
(b) (4) FEI: (b) (4)	<ul style="list-style-type: none"> • Manufacturing of DP (syringe filling and stoppering) • Release of DP (endotoxin testing)

Facility and Identification	Responsibilities
DUNS: (b) (4)	
(b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none"> Visual Inspection of DP (PFS)
Bavarian Nordic A/S (b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none"> Release of DF and FDP
(b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none"> Manufacturing of FDP (final assembly, labeling and packaging)
(b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none"> DP release testing (b) (4)
(b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none"> BDP release testing (b) (4)

Facility and Identification	Responsibilities
(b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none">DP release testing (sterility testing)
(b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none">CCIT on DP and FDP (for stability studies)
(b) (4) FEI: (b) (4) DUNS: (b) (4)	<ul style="list-style-type: none">DP and FDP release testing for phase 3 clinical trial materials (including sterility testing)

*A PLI of (b) (4) facility was performed (b) (4)

** A PLI of (b) (4) was performed (b) (4)

*** A PLI of (b) (4) was performed (b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.3.1

☐ The information provided in this section is acceptable as submitted.

3.2.P.3.3 Description of Manufacturing Process

Manufacturing of CHIKV BDP

(b) (4)

(b) (4)

Manufacturing of CHIKV DP (Bulk Packaged PFS)

The applicant summarized the CHIKV DP manufacturing processing steps (including syringe filling and stoppering, visual inspections, and bulk packaging) as the following:

- The BDP (b) (4) is inspected upon the receipt at (b) (4) for any leaks and damages. If the (b) (4) has no visual defects, BDP is stored at (b) (4) until further processing into CHIKV DP.
- The syringe filling line Grade (b) (4) system is decontaminated using the (b) (4) process per the (b) (4) current procedure (b) (4)

Review Comments: During the PLI of (b) (4) it was noted that the Grade (b) (4) system consists of (b) (4)
(b) (4)

- Prior to the syringe filling, (b) (4) BDP (b) (4) is (b) (4) (b) (4) The BDP (b) (4) is aseptically connected to the product recirculation lines and to a (b) (4) assembly. The (b) (4) is aseptically connected (through RTP) to filling

machine inside a Grade (b) (4) (see Figure 4 of 3.2.P.3.3 of STN 125820/0.2 for diagram of connection of BDP (b) (4) to syringe filling line).

Review Comments: The aseptic connections of the BDP (b) (4) with the filling line appeared acceptable. During the PLI of (b) (4) facility (for the manufacture of BDP), it was confirmed that all aseptic connectors for connecting BDP (b) (4) to recirculation lines, to (b) (4) and to the filling line are single use. Once connected, the assembled filling system is considered closed to allow syringe filling (an open operation) being conducted aseptically in Grade (b) (4). If the Grade (b) (4) environment is compromised after the connection of the filling system is completed, the sterility assurance of the assembled filling system is considered compromised, thus, no further processing of remaining BDP can be conducted (see the review of (b) (4) 483 responses, the CBER IR #38 and responses).

- The filling line has a set of the filling needles that fills two syringes at a time (a validated filling speed is about (b) (4)). The syringe fill line is purged with (b) (4) (a total of (b) (4) syringes, (b) (4) syringes per filling needle) at the (b) (4) of filling or (b) (4) the filling line is restarted after stoppage if stoppage time is (b) (4) or (b) (4) syringes per filling needle if stoppage (or recirculation line shutdown) time is between (b) (4). A fill (b) (4) calibration is performed on about (b) (4) filled syringes at the (b) (4) of filling.

Review Comments: In Table 3 of 3.2.P.3.4 of STN 125820/0.2, the applicant summarized DP filling process critical process parameters, CPP (including filling line (b) (4) and fill (b) (4)). The defined DP filling CPP appeared acceptable.

- Sterile RTU plunger stoppers are transferred to the (b) (4) via RTP alpha port. All filled syringes are automatically stoppered to a pre-set depth in the syringe before exiting the (b) (4).
- Filled and stoppered PFSs are nested in tubs with tub lids, and stored inverted (i.e., tip cap facing up) at 2 – 8°C until transferred to (b) (4) for visual inspection (VI).
- All DP PFSs are subjected to VI by trained personnel. The applicant listed all defect types for CHIKV DP VI in the Table 1 of Section 3.2.P.3.3 of STN 125820/0.2. Defects were classified as critical (e.g., no solution in syringe, Luer lock not attached to the barrel, or fracture penetrated through syringe glass wall), major (e.g., small fracture in the glass did not penetrate the syringe glass wall) or minor (e.g., cosmetic damage).
- Samples of PFS units which passed manual VI are randomly selected for a statistical acceptance quality level (AQL) inspection by certified QA inspectors. Because CHIKV DP (PFS) is a new product manufactured at (b) (4) the initial defect limits (for the first (b) (4) lots) were summarized in the table below. The limits will be trended, and alert and action limits after (b) (4) lots will be established with (b) (4) standard deviations.

Table 5. PFS Alert and Action Limits

Defect Type	Alert Level (%)	Action Level (%)
Critical	(b) (4)	(b) (4)
Major	(b) (4)	(b) (4)
Minor	(b) (4)	(b) (4)

- Tubs with CHIKV DP PFS are sealed with lids and then taped shut, labelled, and placed in shipping case (tubs/case) using a 4-cell partition (1 tub per cell, any empty cell is filled with dunnage). The shipping cases are palletized (with 4 case per layer and up to 7 layers (28 cases) per pallet. Bulk packaged PFSs are stored at 2 – 8°C until shipped to (b) (4) for the labeling of FDP.

Review Comments: The defined defect types for DP PFS VI appeared acceptable. The DP PFS release testing includes sterility (acceptance criteria: No growth), endotoxin (acceptance criteria: (b) (4) and (b) (4) for syringe functionality. CCIT is (sterility and endotoxin are not) tested for DP stability. Noted sterility and endotoxin were tested for the release of DP PFS (as the initial time point, T0). The DP 2 – 8°C long-term storage (≤36 months) was supported by stability data of phase 3 batches (including (b) (4) sterility and CCIT results). The long-term stability study of DP PPQ batches is ongoing. DMPQ defers to DVP to evaluate the adequacy of DP quality release testing results and specifications.

Manufacturing of CHIKV FDP (individually labelled and package DP PFS)

The applicant stated that the insertion of plunger and labeling of syringe are performed by an automated syringe assembly and labeling machine, and that the addition of the finger flange and the packaging of syringe in a pre-labelled carton are performed manually by operators, including:

- The unlabeled CHIKV DP PFSs are equilibrated at (b) (4) and manually loaded onto the in-feed of an automated syringe assembly and labeling machine.
 - The machine operates at a line speed of (b) (4)
 - A plunger rod is inserted.
 - A camera checks for the presence and the position of the plunger rod.
 - Defective syringes are rejected by the machine.
 - A label is applied to each syringe, and the label is checked by (b) (4) cameras: (1) to scan the label prior to application to verify the correct lot number and expiry date, and (2) to verify the presence of label on the labelled PFS.
 - Defective syringes are rejected and moved to waste container.
- The passing syringes are moved to the outfeed rail and are manually removed from the outfeed conveyor, visually inspected by operators, and the finger flange is manually fitted.

- Secondary packaging includes individually placing a fully assembled syringe into a tray by (b) (4) operator and verified by a (b) (4) operator. The tray is then placed in a pre-labeled carton with the package insert, closed and sealed.
- Cartons are packed into the shipper box. A label is applied to the shipper. Each shipper is weighed to verify content. The shippers are then palletized and stored at 2-8°C until shipment to distributors.
- AQL sampling and inspection of the syringe, tray and shipper box are performed at the end of each batch.
- A time out of refrigeration (TOR) of (b) (4) has been established for FDP assembly and packaging.

Review Comments: The applicant indicated that identity (by (b) (4)) is tested for FDP release. The FDP 2 – 8°C long-term storage (≤36 months) was supported by stability data of phase 3 batches (including (b) (4) and CCIT results). The long-term storage stability of FDP PPQ batches is ongoing. DMPQ defers to DVP, DBSQC and device reviewers to evaluate the adequacy of FDP release testing results and specifications.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- ☐ The information under the DMPQ purview appears acceptable as submitted.
- ☐ No reprocessing of BDP, DP, or FDP is performed.

3.2.P.3.4 Controls of Critical Steps and Intermediates

DMPQ defers to DVP reviewers to review this section.

3.2.P.3.5 Process Validation and/or Evaluation

Manufacturing of CHIKV BDP

Review Comments: DMPQ defers to DVP reviewers to review and evaluate BDP PPQ data for product quality attributes and results in Section 3.2.P.3.5. The facility and equipment qualifications (autoclave, (b) (4) decontamination, hold timed and medial fill) were reviewed in Section 3.2.A.1 (b) (4) facility. The aseptic process simulation (for sterile filtration of (b) (4)) and validation of shipment of BDP from (b) (4) facility to (b) (4) facility were reviewed below.

BDP Process Performance Qualification (PPQ) Batches

Review Comments: The applicant summarized information of three BDP PPQ batches (e.g., (b) (4)) in Table 1 of Section 3.2.P.3.5 of STN 125820/0.2, and all in-process testing (IPT) results in Tables 2 – 7 of Section 3.2.P.3.5 of STN 125820/0.2, demonstrating that all testing results met specifications, including IPT under the DMPQ purview, e.g., BDP hold time and the Grade (b) (4) Environmental Monitoring (EM) results (e.g., (b) (4)). There were no microbial deviations during the manufacture of

1 page has been determined to be releasable: (b)(4)

(b) (4)

Manufacturing of CHIKV DP

Review Comments: DMPQ defers to DVP reviewers to review and evaluate DP PPQ (batches (b) (4)) data for product quality attributes and results in Section 3.2.P.3.5. The sterility, endotoxin, and EM testing results (non-viable and viable counts for Grade (b) (4) and Grade (b) (4) all met acceptance criteria (Section 3.2.A.1 for EM limits). The facility and equipment qualifications (autoclave, (b) (4) decontamination, and aseptic process simulation by media fill) were reviewed in Section 3.2.A.1 (b) (4) facility. The aseptic process simulation (for the manufacture of DP) was audited during the PLI of (b) (4). The validation of shipment of DP from (b) (4) facility to (b) (4) was reviewed below.

DP PPQ lots

Review Comments: The applicant summarized information of three DP PPQ batches (including batches (b) (4)) in Table 8 of Section 3.2.P.3.5 of STN 125820/0.2, and all in-process testing (IPT) results in Table 9 of Section 3.2.P.3.5 of STN 125820/0.2, demonstrating that testing results met specifications, including the sterility and endotoxin testing results, the Grade (b) (4) EM results (e.g., (b) (4)).

(b) (4) *Several minor deviations with no impact on product quality were encountered and were resolved during the execution of DP PPQ runs. There were no microbial deviations during the manufacture of the DP PPQ batches. The applicant concluded that the DP manufacturing process is validated for the commercial production of CHIKV DP (PFS) at (b) (4) DMPQ defers to DVP to further review product quality IPT testing results and specifications. The DVP reviewer mentioned that the applicant committed to submit the DP shipping validation data post approval of this BLA as a post-marketing commitment.*

Simulated Shipping Validation of DP from (b) (4) to (b) (4)

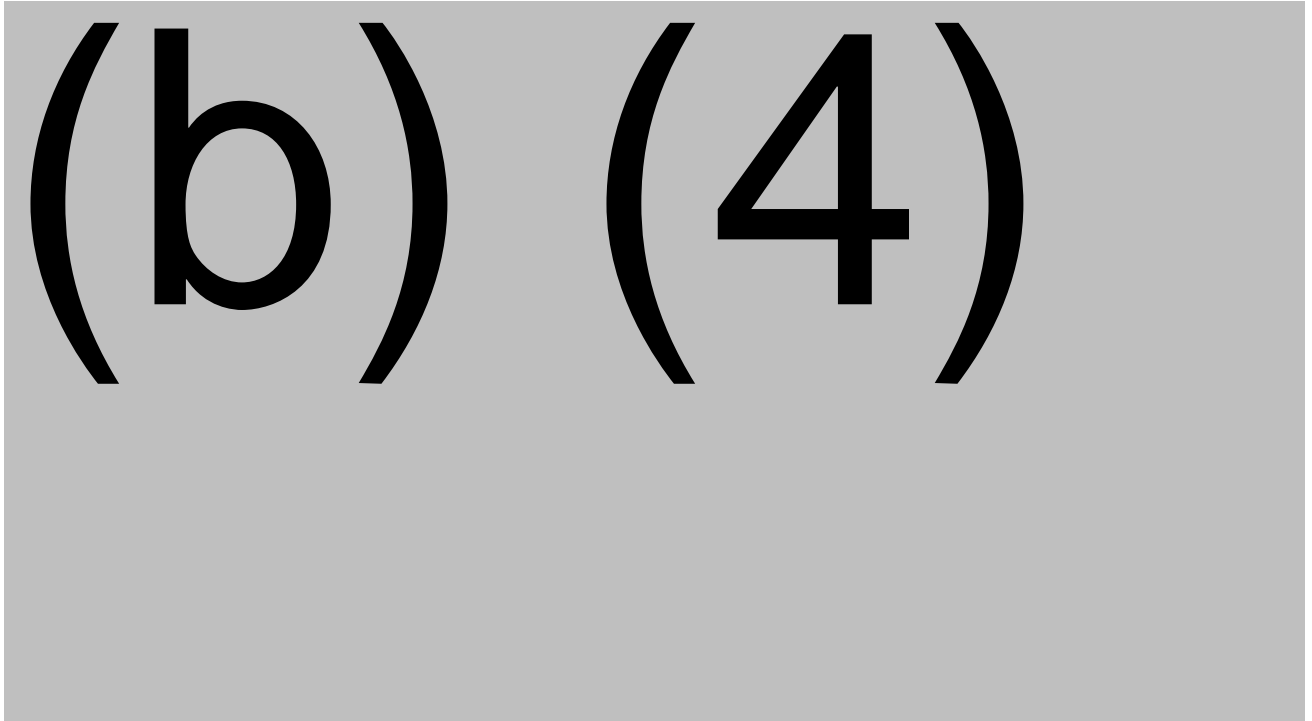
In Table 31 of Section 3.2.P.3.5 of STN 125820/0.2, the applicant described and illustrated packaging configuration for CHIKV DP PFS (same as reviewed above in the description of DP manufacturing processing steps). The applicant stated that a simulated shipping validation (using engineering lots of CHIKV DP PFS which had the same CCS as the commercial batches of PFS) to evaluate the impact of (b) (4) and (b) (4) on DP shipped from (b) (4) was performed:

(b) (4)

***Review Comments:** The material positions in the pallet for DP simulated transportation appeared acceptable. The standard (b) (4) testing, including (b) (4) testing for mechanical handling, (b) (4) testing for simulate (b) (4) (b) (4) during transportation, appeared acceptable. The testing on the shipped PFS under the DMPQ purview (including CCIT and (b) (4) appeared acceptable. DMPQ defers to DVP and CBER device reviewer to evaluate the necessity and adequacy of additional tests.*

DP Transportation Simulation Testing Results

The applicant summarized the transportation simulation study results as the following:



Visual Inspection and CCIT Results of Shipped DP PFS

The applicant summarized visual inspection results in Figure 24 of Section 3.2.P.3.5 of STN 125820/0.2, including:

- In the initial (b) (4) test, shipper box did not pass the post-shipment visual inspection because major and minor defects (e.g., (b) (4) (b) (4) exceeded limits, but the critical defect was within the acceptance limit. The applicant stated that (b) (4) pallet variants (b) (4) (b) (4) were used to repeat the (b) (4) test per (b) (4) (b) (4) using the materials (shipper cases) that were used in the original pallet for (b) (4) test. (b) (4) pallet variants passed the (b) (4) test.
- All shipped Syringe tubs passed visual inspection (for critical, or major, or minor defects).
- All shipped PFS passed visual inspection (for critical, or major, or minor defect).

- (b) (4) PFSs (of (b) (4)) were tested for container closure integrity (CCI) using a validated (b) (4) method. (b) (4) syringes from batch (b) (4) were tested as control group (e.g., negative controls, positive controls). The CCIT results showed that CCI was maintained in all (b) (4) tested PFSs.

The applicant stated that the pallet (with the original pallet configuration) tipping over most likely caused damages to shipper boxes (resulting major and minor defects) but had no impact on the quality of PFS and syringe CCI as showed by the CCIT results. The (b) (4) improved pallet variants will be used for commercial CHIKV DP PFS shipping validation (PMC#4).

(b) (4) Results of Shipped DP PFS

The applicant stated the following:

- A total of (b) (4) syringes of (b) (4) were tested for (b) (4) and (b) (4) syringes from batch (b) (4) were used as control group.
- The (b) (4) testing results (see Tables 33 and 34 of Section 3.2.P.3.5 of STN 125820/0.2).

Review Comments: The above reviewed simulated shipping validation (using engineering lots in lieu of PPQ lots) results appeared acceptable to support the shipment of CHIKV DP PFS from (b) (4) to (b) (4)

Noted, the applicant provided a transportation validation protocol for CHIKV DP PFS transport from (b) (4) to (b) (4). The operational qualification (OQ) results of (b) (4) appeared acceptable. The DMPQ defers to DVP and CBER device reviewers to review additional shipping validation results (including shipping stress stability study results) to evaluate the adequacy of additional shipping operational qualification results. Per the DVP reviewer request, the applicant committed to submit DP transportation validation data using the PPQ lots by February 28, 2026 (PMC #4).

Manufacturing of CHIKV FDP

Review Comments: The applicant summarized information of three FDP PPQ batches in Table 20 of Section 3.2.P.3.5 of STN 125820/0.2, and all process parameter results were summarized in Tables 21 - 25 of Section 3.2.P.3.5 of STN 125820/0.2, demonstrating that testing results met specifications, including syringe (b) (4) sterility, and CCIT. No deviations were encountered during the manufacture of the FDP PPQ batches. DMPQ defers to DVP to further review product quality IPT testing results and specifications.

The applicant did not provide shipping validation data for FDP PPQ batches manufactured by (b) (4). The applicant provided limited FDP shipment results (including (b) (4), CCI, sterility and endotoxin) from (b) (4) (manufactured by a different

manufacturer) and showed that all testing results met specifications. Per the DVP and device reviewers' request, the applicant committed to submit the final FDP shipping validation results by June 30, 2025, as a post-marketing commitment. DMPQ defers to CBER device reviewer to evaluate the adequacy of additional shipping study results (of design verification study and DP quality data) and FDP shipping validation protocol.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- ❑ The information provided in this section under the DMPQ purview appeared acceptable as submitted.
- ❑ CBER (DVP and device reviewers) sent an IR to request the shipping validation information of FDP.

3.2.P.5 Control of Drug Product**3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)**

DMPQ defers to DVP reviewers to review this section.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**CCIT on DP PFS**

The applicant provided information of CCIT by (b) (4) method in Section 3.2.P.5.2 and the information of CCIT method validation in Section 3.2.P.5.3. The validated CCIT by (b) (4) method (using positive controls with a defect (b) (4) appeared acceptable.

CCIT Procedure: (b) (4)

Controls: (b) (4)

Validity: (b) (4)

Acceptance criteria: All tested syringe samples must be negative (b) (4)
(b) (4)

***Review Comments:** The CCIT method and the method sensitivity appeared adequate. DMPQ defers to DVP and DBSQC to review additional analytical procedures for testing the DP quality parameters.*

3.2.P.5.4 Batch Analyses

***Review Comments:** The batch analyses results under the DMPQ purview include:*

- *Sterility and endotoxin testing results for (b) (4) PPQ batches and for DP PPQ batches.*
- *Sterility, CCIT by (b) (4) method, and syringe (b) (4) testing results for FDP PPQ batches.*

The submitted batch analyses results under the DMPQ purview for (b) (4) PPQ batches and post-PPQ batches in Tables 6 and 7 of Section 3.2.P.5.4 of STN 125820/0.2, for DP PPQ batches in Table 10 of Section 3.2.P.5.4 of STN 125820/0.2, and for FDP PPQ batches in Table 12 of Section 3.2.P.5.4 of STN 125820/0.2. All batches met acceptance criteria for sterility, endotoxin, CCIT, and syringe (b) (4) testing. DMPQ defers to DVP to evaluate other DP quality testing results.

3.2.P.7 Container Closure System (CCS)

The Applicant provided the CCS information (description, specification, and drawings) of CHIKV BDP and DP in Section 3.2.P.7 of STN 125820/0.2, including:

The BDP container closure system consists of a (b) (4)

(b) (4) As reviewed in BDP shipping validation, the integrity of (b) (4) (b) (4) can be maintained after being handled during the routine manufacturing operations (including BDP storage and shipment, and DP manufacturing processing steps).

The CHIKV DP is provided in PFS and is classified as a single-entity drug/device combination product.

The CHIKV DP container closure system consists of the Type (b) (4) glass barrel, Luer lock adapter, rigid cap, and rubber closure (b) (4) with Luer lock System), and a rubber plunger stopper as illustrated in Figure 1 of Section 3.2.P.7 of STN 125820/0.2 for PFS components. Noted, to manufacture CHIKV DP PFS at (b) (4) DP is aseptically filled into pre-assembled sterile syringe (with syringe barrel, luer lock adapter and cap), and aseptically stoppered with sterile plunger stopper.

The filled and stoppered CHIKV is shipped from (b) (4) where a plastic plunger rod is attached to the rubber plunger, and a plastic finger flange is added to produce the CHIKV FDP.

Review Comments: The CCI of CHIKV DP and FDP is tested by using a validated (b) (4) based CCIT method. CCIT is tested for DP and FDP stability. DMPQ defers to DP and CBER device reviewers to evaluate the suitability of DP CCS and components, and the compliance to regulatory requirements for combination product.

Overall Reviewer's Assessment of Section 3.2.P.7:

- ☐ The information provided in this section appeared acceptable as submitted.

3.2.P.8 Stability**3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data**

The applicant indicated that the CHIKV (b) (4) DP, and FDP stabilities have been monitored under the long-term (2 – 8°C), or accelerated (b) (4) (b) (4) (b) (4) (b) (4) DP only) storage conditions, including:

(b) (4)

- DP (stored at 2 – 8°C for up to (b) (4) months) or accelerated (b) (4) for up to 6 months). The applicant provided the information of all DP stability batches in Table 5 of Section 3.2.P.8.1 of STN 125820/0.2. Sterility is tested for DP release and for accelerated stability, and CCI is tested for DP long-term stability.

The long-term stability of (b) (4) DP PPQ batches (b) (4) and is ongoing. The applicant stated that there was no change in sterility and/or CCI of DP (clinical materials and PPQ batches) under long-term (up to 36 months for clinical materials) or accelerated storage conditions (up to 6 months for clinical materials).

The applicant proposed the shelf time for DP as 36 months (2 – 8°C).

- FDP is stored at 2 – 8°C for up to (b) (4) months. The applicant provided the information of all FDP stability batches in Table 9 of Section 3.2.P.8.1 of STN 125820/0.2. Sterility is tested for DP release and for FDP PPQ stability at time points (e.g., T-36, (b) (4), and CCI is tested for FDP long-term stability at T-0 and T-24. The applicant indicated that, the sterility, CCI and (b) (4) tests

are performed for FDP stability, however, at the time of submission, beside the FDP release data (T0), there was no stability data for PPQ batches.

Review Comments: The provided stability testing results under the DMPQ purview appeared acceptable. DMPQ defers to DVP to review additional product quality testing results and to evaluate the adequacy of proposed shelf life for (b) (4) DP and FDP.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (b) (4)

(b) (4)

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.A.1 Facilities and Equipment (b) (4) – Manufacturing DP in PFS)

Overview of (b) (4) CHIKV Manufacturing Facility and Manufacturing Areas

(b) (4)

HVAC System and EM Program in (b) (4) Facility

The HVAC system for cleanroom areas includes a combination of AHUs to supply temperature and humidity-controlled air into a common plenum above the cleanroom areas and HEPA fan filter units (FFUs) located in the ceilings of each cleanroom to recirculate the air within each cleanroom. FFU HEPA filters for the filling suite (b) (4) (b) (4) are certified every (b) (4). The (b) (4) serve Grade filling (b) (4) suites (b) (4) and Grade (b) (4) cleanroom areas, and (b) (4) (b) (4) serve the (b) (4).

In Table 2 of Section 3.2.A.1 (b) (4) STN 125820/0.2, the applicant provided information of (b) (4) production rooms, including room number, name/use, and cleanroom classification. The filling (b) (4) is inside Grade (b) (4) in filling suite room (b) (4) (Grade (b) (4)).

The EM program monitors viable and non-viable particulates. The applicant summarized information of EM testing requirement and acceptance criteria (for cleanroom areas and personnel) in Tables 3 – 5 of Section 3.2.A.1 (b) (4) of STN 125820/0.2. The (b) (4) classified cleanroom EM was performed per the firm SOP (SOP-0549). NVP specifications for classified cleanroom areas (Grade (b) (4)) were the same as specifications listed in Table 5 above. The NVP specifications for Grade (b) (4) cleanroom areas were not defined under in-operation conditions. The (b) (4) VP specifications for classified cleanroom areas were summarized in table below.

Table 9. (b) (4) Alert and Action Limits

(b) (4)	(4)
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Review Comments: The submitted HVAC AHU Zones, airflows and air pressurization, flows (including personnel, material, finished DP, and waste) were reviewed and verified during the PLI of (b) (4). The HVAC system and EM program appeared acceptable. The (b) (4) classified cleanroom EM program and EM specifications appeared acceptable. No objectionable issues were identified.

Major Equipment Validations

Review Comments: *I reviewed the following major equipment validations and did not identify objectionable issues:*

(b) (4)

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

(b) (4)

3.2.A.1 Facilities and Equipment (b) (4) – Labeling and Packaging)

(b) (4) is a contract packager located in (b) (4). (b) (4) packages pharmaceutical, biotechnology, and combination products in various forms, including vials, and syringes.

The unlabeled CHIKV DP bulk PFSs were shipped from (b) (4) using qualified (b) (4). The FDP manufacturing steps performed at (b) (4) include automated labelling of the CHIKV VLP drug product (DP), mechanical insertion of the plunger rod, manual attachment of the finger flange, and manual packaging in the final labelled tray and carton.

The FDP manufacturing (labelling and packaging) areas are controlled environments, having have terminal HEPA filtration units to provide temperature (b) (4) and humidity (b) (4) controlled and monitored clean air. The FDP manufacturing areas are classified as controlled but not classified (CNC) and have a positive pressure differential in relation to the secondary rooms and adjacent corridors.

The major manufacturing equipment used in the CHIKV FDP manufacturing process include an (b) (4) syringe labeler and (b) (4). The equipment was qualified by (b) (4) per internal procedures. The applicant stated that an engineering labeling study and a PQ were executed on syringe labeler prior to the manufacture of the CHIKV FDP PPQ lots. As reviewed in Section 3.2.P.3.5, the applicant provided satisfactory results for the CHIKV PPQ lots, including CCIT and (b) (4) testing results, indicating that the FDP manufacturing processing steps and equipment were validated for the intended uses.

There is no specialized water supply system in (b) (4) facility because water is not used in the packaging processes.

Review Comments: The information provided in Section 3.2.A.1 (b) (4) of STN 125820/0.2 appeared acceptable. No objectionable issues were identified.

Overall Reviewer's Assessment of Section 3.2.A.1:

- ☐ The information provided in Section 3.2.A.1 appears acceptable as submitted.

3.2.R Regional Information (USA)

Combination Products

Review Comments: The CHIKV DP is filled as single dose in 1 mL PFS and is classified as a single-entity drug/device combination product. DMPQ reviewed Purchasing Controls, CAPA and Risk Analysis. No objectionable issues were identified. DMPQ defers to the CBER device reviewer to further evaluate the compliance to the regulatory requirements for the combination products.

Purchasing Controls

In Section 3.2.R Regional Information – Medical Device [CHIKV VLP DP, Suspension for injection] of STN 125820/0.2, the applicant stated the following:

- All Bavarian Nordic suppliers undergo a supplier evaluation per internal SOPs prior to adding to the approved supplier list.
- Responsibility for the qualification and management of suppliers for the PFS components were defined in Bavarian Nordic internal quality group SOPs.
- Suppliers are re-evaluated on a routine basis, in accordance with internal SOPs.

Review Comments: The applicant's purchasing controls appeared acceptable. No objectional issues were identified.

Corrective and Preventive Action (CAPA)

The applicant stated the following:

- The Bavarian Nordic deviations SOP outlined the process for initiating, documenting, investigating and escalation of internal deviations derived from within the Bavarian Nordic Quality Management System (QMS) and external deviations specific to quality events derived from CMOs and contracted suppliers of goods/services, as required.
- The deviation SOP listed the requirements for handling of corrective and preventive actions (CAPA) to initiate, document, approval, track, and close CAPA (when needed). The CAPA was part of Bavarian Nordic's continuous improvement and the CAPA effectiveness was checked.

Review Comments: *The applicant's CAPA managements appeared acceptable. No objectionable issues were identified.*

Risk Analysis

The applicant stated that the combination product is intended to be used by healthcare professionals only and does not have a device constituent part for which human factors (HF) data should be submitted per the Draft Guidance for Industry: *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*.

The applicant stated that a User-Related Risk Assessment (URRA) and Mitigation of User Risk for the PFS configuration was completed and was submitted to CBER in the Type C Meeting Request (November 12, 2020, BB-IND 17998; Sequence No. 0043), and that CBER agreed (in the CBER written response, February 02, 2022) that a HF validation study was not needed for licensure based on the URRA.

Review Comments: *No objectionable issues were identified.*