

CBER BLA Device Review Memorandum – Prefilled Syringe (PFS)

BLA STN 125820

VIMKUNYA [Chikungunya Vaccine, Recombinant]

**Andrea Gray, PhD
CBER/ORO/DROP/RPB**

1. BLA STN

125820

2. APPPLICANT NAME

Bavarian Nordic A/S

3. PRODUCT NAME/PRODUCT TYPE

- Non-Proprietary/Proper/USAN: Chikungunya Vaccine, Recombinant
- Proprietary Name: VIMKUNYA

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- General Description: sterile aluminum hydroxide-adjuvanted vaccine in a prefilled syringe
- Route of administration: Intramuscular
- Indication(s): Prevention of disease caused by chikungunya virus infection in individuals 12 years of age and older

5. COMBINATION PRODUCT INFORMATION

- Type: 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)
- Biologic Constituent(s): Vaccine
- Drug Constituent(s): n/a
- Device Constituent(s): prefilled syringe

6. MAJOR MILESTONES

- Filing Meeting: July 29, 2024
- Midcycle Internal Meeting: September 30, 2024
- Late Cycle Internal Meeting: November 19, 2024
- PDUFA Action Date: February 14, 2025

7. QUALITY REVIEW TEAM

Reviewer/Affiliation	PFS-Relevant Subject Matter
Shufeng Liu CBER/OVRR/DVP/LVBD	Product compatibility, drug product quality attributes including sterility and endotoxin, container closure considerations (e.g., extractables/leachables and toxicological risk assessment, particulates)
Wei Wang CBER/OCBQ/DMPQ/MRB3	Container closure integrity testing, aseptic processing, sterilization, depyrogenation, shipping validation (CCIT, plunger stopper movement), QMS (management responsibility, CAPA)

8. INTRA- & INTER-CENTER CONSULTS

none

9. SUBMISSION(S) REVIEWED

Date Received	eCTD Sequence	Amd (STN 2 nd Level)	Comments
17 June 2024	0003	0	Final rolling submission module (CMC)
13 Nov 2024	0039	38	Updated stability data
06 Dec 2024	0049	48	Response to device IR#40

10. RELEVANT REFERENCED REGULATORY SUBMISSIONS

Submission Type & STN (Center)	Holder	Referenced Information	Letter of Authorization (Yes/No)	Comments/Status
(b) (4) (CDER)	(b) (4)	(b) (4) syringe subassembly (barrel, (b) (4) lubricant, luer lock adaptor, tip cap, rigid cap)	yes	Recent MF review leveraged from BLA 125770. No new device review memo needed.
(b) (4) (CBER)	(b) (4)	Plunger stopper material	yes	Relevant information provided by Applicant in response to IR#40. No memo generated.
(b) (4) (CBER)	(b) (4)	Plunger stopper (b) (4) sterilization process	yes	Any necessary review deferred to DMPQ. No device review memo created.
(b) (4) (CBER)	(b) (4)	Plunger stopper (b) (4) in preparation for sterilization	yes	Any necessary review deferred to DMPQ. No device review memo created.

11. RELEVANT PRIOR INTERACTIONS

- 02 February 2022 –response to HF questions in IND 17998.42
 - No HF validation study needed
 - CDER/.../DMEPA consult [ICCR # 00813964](#)
 - Response and consult memo available in CBER Connect
- 25 January 2024 – IND 17998.110 pre-BLA written responses (CMC/product)
 - Included comments on device information to include in the BLA
 - Response available in CBER Connect

12. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Bavarian Nordic A/S submitted BLA 125820 for licensure of their Chikungunya Vaccine, Recombinant (VIMKUNYA), which consists of the drug product filled into a prefilled syringe (PFS) consisting of a Type (b) (4) glass syringe barrel with a luer lock adapter and rigid cap, chlorobutyl rubber plunger stopper, polypropylene finger flange and plunger rod. The scope of this review memo includes: PFS description, PFS design verification (including device essential performance, e.g., deliverable volume, (b) (4) (b) (4) verification of device essential performance over the proposed shelf life and after shipping, control strategy to ensure the final combination product meets essential performance requirements, PFS biocompatibility, and compliance with applicable device quality system regulations (design controls regulations (21 CFR 820.30), purchasing control regulations (21 CFR 820.50)).

B. RECOMMENDATION

I. APPROVAL

There is one device-relevant non-506B postmarketing commitment (PMC), communicated to the applicant on January 16, 2025, and acknowledged by the applicant on January 22, 2025 (see “Advice” telecon records dated January 22, 2025, in CBER Connect):

- You commit to conduct Finished Drug Product (FDP) transport validation studies (b) (4) as described in section 3.2.P.3.5 (2.5.3.3) of your BLA 125820/0. The final study report will be submitted by June 30, 2025, as a “PMC Submission – Final Study Report.”

II. SIGNATURE BLOCK

Reviewer, Title, Affiliation	Concurrence	Signature and Date
Andrea Gray, PhD Device/Combination Product Reviewer CBER/ORO/DROP/RPB	-	
Cherie Ward-Peralta, MS, RAC Branch Chief CBER/ORO/DROP/RPB	Concur (January 31, 2025)	

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I. Product Description

A. Combination Product

The combination product consists of the drug product filled into a prefilled syringe (PFS) consisting of a Type (b) (4) glass syringe barrel with a luer lock adapter and rigid cap, chlorobutyl rubber plunger stopper, polypropylene finger flange and plunger rod. Applicant acknowledges the CHIKV VLP Vaccine PFS is classified as a single-entity drug/device combination product.

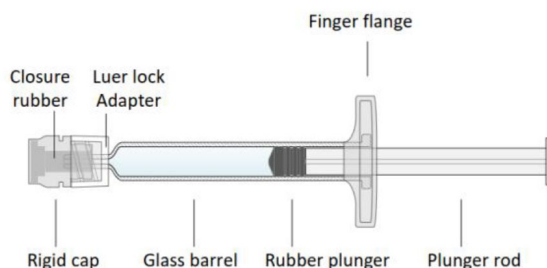
B. Drug/Biologic

The Chikungunya Virus Virus-Like Particle (CHIKV VLP) Vaccine is a sterile aluminum hydroxide-adjuvanted drug product (DP). Module 3.2.P.3.2 Batch Formula states the (b) (4) of the DP is (b) (4). Notably, Module 3.2.P.5.4 states “The chikungunya

virus virus-like particle (CHIKV VLP) vaccine was initially developed by the National Institutes of Health (NIH) Vaccine Research Center (VRC). The vaccine was then in-licensed to Emergent BioSolutions (formerly PaxVax, Inc.). After production of the phase 3 clinical trial material (CTM), the program was acquired by Bavarian Nordic A/S.” Refer to CMC memo for additional information on the drug product.


C. Syringe

Figure 1: CHIKV VLP Pre-Filled Syringe



From Module 3.2.R Regional Information – Medical Device

Table 7: CHIKV VLP Prefilled Syringe Component Description

	Component	Product Contact	Description	Manufacturer
	Rigid cap	No	(b) (4)	
	Closure	Yes		
	Glass barrel	Yes		
	Luer lock adapter	No		
	Rubber plunger	Yes		
	Plunger rod	No		
	Finger flange	No		

From Module 3.2.P.2.4. Container Closure System

Module 3.2.P.2.4. Container Closure System states “The PFS is intended to be used by healthcare professionals (HCPs) only to administer a single dose to a single patient

within a clinical setting... The transparent label and clear, glass barrel of the PFS enables visual inspection to ensure adherence to (b) (4) and 21 CFR 201.57(c)(3)(iv) requirements for the dosage and administration for parenterals.”

Components and Suppliers	See table above
Connection Type	Luer lock
Intended Connector(s)	Needle
Materials of Construction	See table above <i>Reviewer Comment: Notably, Section 1.2.4.2 in Module 3.2.P.2.4 Container Closure, in the context of extractables and leachables information, states (emphasis added by reviewer) “The rubber plunger used for the syringe is made of (b) (4) with (b) (4). This distinction is relevant to the review of biocompatibility in Section V of this memo.</i>
Dimensions	Engineering drawings provided in Module 3.2.P.7
Syringe Volume	1 mL
Fill Volume	(b) (4) mL
Sterilization Method	Syringes are provided sterile (via (b) (4)) and ready-to-use with pre-assembled components. Stoppers are provided sterile (by (b) (4)) and ready-to-use.
Route of Administration	Intramuscular injection
Administration Site	Injection site necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per ACIP guidelines .”
Target Tissue and Depth	Target tissue and depth necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per ACIP guidelines .”
Type of Use	single use
Storage Conditions and Proposed Expiry	2°C to 8°C, 36 months
Intended User(s)	Healthcare professionals
Intended Use Environment	Clinic
Needle Length, Gauge, Tip Style	n/a - No needle is included with the packaged syringe. The PFS is connected to the appropriately identified needle for intramuscular (IM) administration prior to use.

Markings	n/a
Reuse Durability	n/a
Safety Features	n/a
Automated Functions	n/a

Table 4 in Module 3.2.P.7 provides the following additional information (excerpted):

Component	Conformance/DMF
Glass barrel, 1 mL long (b) (4)	(b) (4)
Luer lock adapter (b) (4)	
Rigid cap (b) (4)	
Rubber closure (b) (4)	
Rubber plunger stopper	
Plunger rod	
Finger flange	
(b) (4) components assembled by (b) (4)	

Reviewer Comment: Letters of Authorization (LOAs) for the referenced master files are provided in Module 1.4.2.

Reviewer's Overall Assessment and Recommendations: Product description is acceptable.

II. Manufacturing

A. Manufacturers

From Module 3.2.P.3.1 (device-relevant responsibilities indicated in bold added by reviewer):

Facility	Responsibility
Bavarian Nordic (b) (4) (b) (4) FEI: (b) (4) DUNS: (b) (4)	Manufacture and release of bulk drug product (BDP) Release and stability testing of BDP, drug product (DP) and finished drug product (FDP) (including Container content)
Bavarian Nordic A/S (b) (4) (b) (4) (b) (4) FEI: (b) (4) DUNS: (b) (4)	Release of DP and FDP
<div style="font-size: 100px; text-align: center;">(b) (4)</div>	Manufacture of DP Release testing of DP
	Visual Inspection of DP
	FDP final assembly, labeling and packaging
	Contract testing laboratory

(b) (4)	Responsibility
	Contract testing laboratory
	Contract testing laboratory (including Container closure Integrity)
	Contract testing laboratory, design verification testing (Syringe Functionality) (b) (4)
	Contract testing laboratory for ongoing Phase 3 clinical trial material DP and FDP stability studies (including Container content)

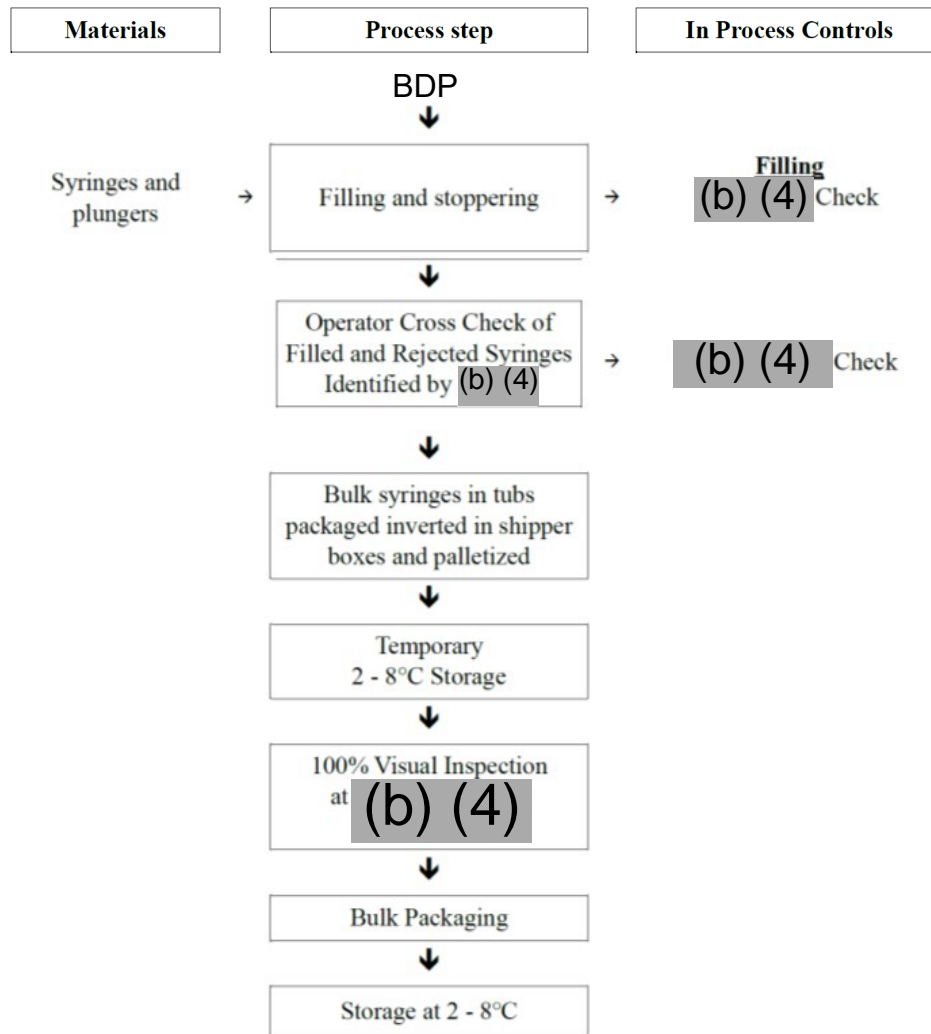
B. Manufacturing Process

Module 3.2.P.3.2 Batch Formula states the validated batch size for chikungunya virus virus-like particle (CHIKV VLP) drug product (DP) is (b) (4)
(b) (4)

Reviewer Comment: BDP = bulk drug product; DP = drug product (in syringe with stopper); FDP = finished drug product (assembled and labeled PFS).

Manufacturing process diagrams including **steps starting from introduction of syringe components for filling** are excerpted below:

Figure 3: Drug Product Manufacturing Process Flow Diagram



From 3.2.P.3.3 Description of the Manufacturing Process and Process Controls

Materials	Process step	In Process Controls
CHIKV VLP DP (unlabeled bulk syringes)	Assembly and labeling	Visual inspection
Plunger rod, syringe label, finger flange		
Tray, carton, package insert, tamper evident seal	Secondary packaging	
Shipper box	Tertiary packaging	
	Storage at 2 - 8°C	

From 3.2.P.3.3 Description of the Manufacturing Process and Process Controls

Introduction of syringe components: "Ready to Use (pre-sterilized) syringe tubs are introduced into the automatic delidder/deliner unit before they are fed individually into the filling unit enclosed in a Grade (b) (4) (decontaminated with (b) (4) (b) (4) (b) (4) ... Stoppers are received ready-to-use from the supplier (packaged with (b) (4) and (b) (4) sterilized) and supplied to the (b) (4) via (b) (4) (b) (4)

Filling: "At the start of filling, the syringe fill line is (b) (4)

The filling machine automatically marks which syringes have been rejected based on unacceptable fill (b) (4)... Filling continues until bubbles appear in the recirculation line indicating a low level of BDP in the (b) (4). At this point, both the filling and (b) (4) are stopped."

Stoppering: "All syringes are also stoppered to a pre-set depth in the syringe before exiting the (b) (4)"

Visual inspection: “The DP, which is now filled in syringes and nested in sealed tubs, is stored inverted (tip cap facing up) at 2-8°C until visual inspection. After line clearance of the visual inspection area, 100% manual visual inspection of the PFS is performed by trained personnel at (b) (4) in inspection booths equipped with (b) (4). Each syringe is inspected for a minimum of (b) (4) each on (b) (4).”

Any defective units are identified with defect type (critical, major, minor), labeled with a red sticker over the syringe flange, segregated for accountability purposes, and rejected.”

Bulk packaging: “Each plastic tub of PFS (100 syringes) is closed with a lid, taped shut, labeled, and placed into a shipping case in the inverted orientation (4 tubs in a case) with a 4-cell partition and a shipper pad. Any empty cells are filled with dunnage. The case configuration is checked by a (b) (4) operator, after which the shipping case is closed, labeled and sealed with packing tape. The shipping cases are then palletized with 4 cases per row stacked up to 7-high (Maximum of (b) (4) PFS).”

PFS Intermediate Storage: “The PFS are stored at 2-8°C until shipment to the final assembly and packaging site (b) (4)

Intermediate Shipping: The PFS pallet is shipped in a qualified refrigerated (b) (4) from (b) (4)

Assembly, Labeling, and Packaging: “The DP is received at (b) (4) (b) (4) and stored at 2-8°C until FDP processing. (b) (4) performs a semi-automated assembly (automated addition of plunger rod, application of label and manual addition of finger flange), labeling, and packaging (secondary and tertiary) process resulting in FDP which is then stored at 2-8°C until shipment to distributors.”

- Labeling: “A label is applied to each syringe which is checked by (b) (4) (b) (4)
- Plunger rod insertion: “A plunger rod is inserted by rotating the syringe barrel at a predefined speed (b) (4) while the plunger rod is inserted downwards into the stopper (height of plunger rod insertion station (b) (4) A (b) (4) checks for the presence of the plunger rod and that it is not too high (loosely fitted). Defective syringes are rejected by the machine.”
- Finger Flange Placement: “The syringes are manually removed from the outfeed conveyor, visually inspected, and the finger flange is manually fitted.”
- Secondary and Tertiary Packaging: “One (1) fully assembled syringe is then loaded into a tray and verified by a (b) (4) operator. The tray is then placed in a pre-labeled carton with the package insert, closed and sealed. Trays are then 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.”

Shipping to Distributors: “The PFS pallet is shipped in a qualified refrigerated (b) (4) from (b) (4) to distributors.”

i. In Process Controls

Reviewer Comment: Only device-relevant controls are covered in this review. See CMC and DMPQ memos for all other controls.

Table 3 in Module 3.2.P.3.4 Controls of Critical Steps and Intermediates contains the following DP filling process parameters that are critical to ensuring the required deliverable volume of each syringe ((b) (4) 0.80 mL).

Parameter	Target	Normal Operating Range	Proven Acceptable range
Target Fill (b) (4)	(b) (4)	(b) (4)	(b) (4)

Table 4 lists the following in process controls for the drug product:

Test	Acceptance Criteria	Method
(b) (4) Check	(b) (4)	(b) (4)

Regarding the **fill (b) (4) check** in process control, Section 1.4.1.1 of Module 3.2.P.3.4 Controls of Critical Steps and Intermediates states “In line measurement of fill (b) (4) is performed on (b) (4)

Table 5 indicates that the parameter of **attachment of finger flange, with a target of (b) (4)** is a critical process parameter because “it is required by the product specification and is **essential for the PFS intended use.**”

ii. Final Product Specifications and Test Methods

Device-relevant specifications included in Table 2 in Module 3.2.P.5.1 Specifications (Seq 0026) excerpted below.

Test	Method	Acceptance Criteria – Release	Acceptance Criteria – Stability
Container content	(b) (4)	(b) (4)	(4)
Container closure integrity			
Syringe functionality for: (b) (4)			

Reviewer Comment: Container content is equivalent to terms such as deliverable volume or extractable volume, which are all measures of dose accuracy. CCIT is included in the table above as it is used as a surrogate for dose accuracy verification in stability studies (i.e., it is reasonable to assume that container content volume will not change if the integrity of the container closure is maintained).

See [Appendix 1](#) of this memo for a review of analytical methods and validation/qualification.

Reviewer Comment: Review of the analytical method and validation of container closure integrity testing (CCIT) is deferred to DMPQ.

These tests are performed on the DP as opposed to the FDP (b) (4)
(b) (4) Applicant provided support for this approach in
Module 3.2.P.5.6 Justification of Specifications, as summarized below:

(b) (4)

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

iii. Batch Analyses

Results for device-relevant specifications from relevant batches (i.e., product in PFS as opposed to vials) provided in Module 3.2.P.5.4 Batch Analyses are reviewed below. The reviewed batches are identified below (excerpted from Table 1 in this module; DOM = Date of Manufacture; (b) (4) = Phase 3 studies).

All reviewed batches met acceptance criteria for container content, (b) (4)
(b) (4)

FDP Batch	FDP DOM	DP Batch	DP DOM	Manufactured for / Clinical Use
(b) (4)				

A graphical representation of the syringe functionality results is excerpted below from Module 3.2.P.5.6 Justification of Specifications.

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

Information Request (IR)#40.4 Date Sent: November 21, 2024 Date/Amd/eCTD Sequence Received: December 6, 2024/48/0049
IR Comment: Section 2.3.1 of Module 3.2.P.3.5 states the following regarding the FDP PPQ studies: “the release and stability testing of the FDP PPQ batches was performed on the assembled drug product (ADP) instead of the FDP level. For future commercial batches the release testing will be performed on the FDP.” The latter statement appears to conflict with the information in Module 3.2.P.5, which indicates that release testing is conducted on the commercial DP (i.e., samples prior to assembly, labeling, and packaging). Per Table 3 in Module 3.2.P.5.1, only identification testing is conducted on the commercial FDP. Please clarify this discrepancy.
Applicant Response: Bavarian Nordic acknowledges the noted discrepancy and have updated Section 2.3.1 of Module 3.2.P.3.5 with this response to clarify “For future commercial batches the release testing will be performed as outlined in Section 3.2.P.5.1”.
Reviewer Comments: <i>Response is acceptable.</i>

The **ADP PPQ batches** are (b) (4) which are described in the [Batch Analysis](#) section of this memo. The batch size of each was (b) (4) PFS. All syringes met in process acceptance criteria for finger flange attachment. All batches also **met criteria for container content and syringe functionality**, as listed below (from Table 22).



No syringe, shipper tray, or shipper box defects were observed upon visual inspection by AQL sampling.

Reviewer’s Overall Assessment and Recommendations: Manufacturing information is acceptable.

III. [Design Verification](#)

Section 1.5 of Module 3.2.R Medical Device US states “The CHIKV VLP vaccine is intended to be connected to off-the-shelf needles in order to operate as intended. Luer lock compatibility is met from syringe component manufacturer stating compliance with (b) (4)

Section 1.7 states “Clinical features of the CHIKV VLP vaccine include (emphasis added by reviewer):

- **Device delivers a sterile dose (b) (4) 0.8 mL via intramuscular injection**
- Device is compatible with the drug product
- **Device is compliant with (b) (4)**

- The delivery system is compatible with OTS (b) (4) or (b) (4) needles
- White cloudy suspension can be accomplished upon vigorous shaking of the PFS
- The clear syringe barrel with a transparent syringe label provides a window for visual inspection of the contents
- The device is not manufactured using material from animal origin
- The delivery system remains functional within (b) (4) shelf-life when stored at (b) (4)

Design verification is described in Section 1.8.2 and Table 3. The full table is re-created in [Appendix 2](#). Essential performance requirements (EPRs) (b) (4) (b) (4) are excerpted below.

Req. ID	Description	Test Method Summary	Acceptance Criteria	Results	Conclusion
(b) (4)					

(b) (4)

Reviewer Comment: Although the acceptance criteria for (b) (4) in place at the time of this study was higher (b) (4) than the commercial final product acceptance criteria (b) (4) the results were well below both sets of limits.

The full Table 3 as well as Table 6 also contain verification information related to non-EPRs, including those tabulated below.

Characteristic	Verification Evidence
(b) (4)	(b) (4)

Information Request (IR)#40.5**Date Sent:** November 21, 2024**Date/Amd/eCTD Sequence Received:** December 6, 2024/48/0049

IR Comment: In Table 3 of Section 1.8.2 of Module 3.2.R Medical Device US, you list design input requirements for the product. DIR-017 (“The device shall have a luer lock compatible with (b) (4)”) and DIR-038 (“The PFS shall have a luer lock compatible with (b) (4)”) appear to be conflicting. DIR-017 requires compatibility per either (b) (4) or (b) (4) whereas DIR-038 requires just (b) (4). 21 CFR 820.30(c) regarding design inputs states “The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements.” Section 1.8.1 indicates that your QMS complies with the 21 CFR 820 regulations including 820.30 for design controls. Section 1.8.1.1 on design controls does not speak specifically to procedures for addressing incomplete, ambiguous, or conflicting requirements. Please confirm that your design control procedures include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. We also recommend that you review your design input requirements and address any incomplete, ambiguous, or conflicting requirements. Please note that confirmation and acknowledgement of the recommendation are necessary to address this comment (i.e., you are not expected to submit any QMS documentation in response to this comment).

Applicant Response: Bavarian Nordic acknowledges that there is a conflict between DIR-017 and DIR-038. The (b) (4) which is stated for DIR-017 is a typo, additionally, as (b) (4) should no longer be stated, DIR-017 will now be redundant to DIR-038 and has therefore been removed from Table 6 in section 1.8.5 in 3.2.R Medical Device US. Bavarian Nordic confirms that the design control SOPs used to create the CHIK requirements include the procedure for addressing incomplete, ambiguous, and conflicting requirements. Section 1.8.1.1 has been updated to include this statement. The updated version of Section 3.2.R Medical Device US has been provided with the responses.

Reviewer Comments: *Response is acceptable.*

Section 1.2.3 of Module 3.2.P.2.4 Container Closure System provides a summary of the testing done to determine the appropriate DP fill volume to assure a PFS delivery volume of (b) (4) 0.8 mL. Applicant performed (b) (4) DP filling runs using BDP development batch (b) (4) using (b) (4) different fill volumes: (b) (4) fill. PFS delivery volumes (b) (4) were determined for (b) (4) fill volumes by (b) (4) different operators using BDP (b) (4) of (b) (4). Several PFS failed the delivered volume specification of (b) (4) 0.8 mL at the (b) (4) fill volume, but all PFS met the specification at the (b) (4) fill volume. The DP fill volume was therefore established as (b) (4) at that time. Notably, the (b) (4) of BDP was later determined to be (b) (4) therefore, the target fill (b) (4) for commercial manufacturing is (b) (4). Deliverable volume is also tested at release, providing additional assurance that the fill volume is sufficient to account for the residual volume of the PFS with needle attached.

As indicated in the table above, the applicant is leveraging some verification information from the suppliers. Section 1.8.2 states “Where appropriate, component manufacturer

information provided sufficient support for certain design requirements. For examples, statements were gathered from relevant component manufacturers regarding compliance to (b) (4)

(b) (4) and PFS shall have a luer lock compatible with (b) (4). The manufacturer provided statement of compliance to (b) (4) and (b) (4). Since sections (b) (4) of (b) (4) refer to (b) (4) (b) (4) for test requirements and test methods, the manufacturer provided statements satisfy the requirements.” Similarly, Section 1.2.2 of Module 3.2.P.7 states (b) (4) (b) (4) and the performance tests required within the standard.”

Reviewer Comment: *The applicant did not include these supplier statements in their BLA. Applicant should provide these statements to serve as objective evidence of verification of these design requirements. See IR#40.6.*

Information Request (IR)#40.6

Date Sent: November 21, 2024

Date/Amd/eCTD Sequence Received: December 6, 2024/48/0049

IR Comment: Section 1.8.2 of Module 3.2.R Medical Device US states “Where appropriate, component manufacturer information provided sufficient support for certain design requirements. For examples, statements were gathered from relevant component manufacturers regarding compliance to (b) (4) (b) (4) compliance to (b) (4) (b) (4) compliance to (b) (4) (b) (4) and PFS shall have a luer lock compatible with (b) (4). The manufacturer provided statement of compliance to (b) (4). However, you did not provide these supplier statements in your BLA. Please provide the supplier statements you are leveraging for these aspects of design verification. This is being requested to serve as objective evidence of verification of design requirements.

Applicant Response: The requested compliance statements from the supplier are included as attachments to this response, see Table 7 below.

Table 7: Compliance statements from the supplier [converted to list here]

(b) (4)

Reviewer Comments: *1mL Round Flange Product package (b) (4) describes the technical features and specifications for (b) (4) sterile syringe with Luer Lock System (b) (4)*

(b) (4)

Reviewer's Overall Assessment and Recommendations: Design verification information is acceptable.

IV. [Design Validation](#)

Design validation information is provided in Section 1.9 of Module 3.2.R Medical Device US. The information discusses human factors considerations for the product. The acceptability of the applicant's rationale that no further HF studies are needed was assessed under the associated IND. The applicant states "The URRA along with a Mitigation of User Risk based on the URRA report was provided to CBER in the Type C Meeting Request 12 November 2020 (BB-IND 17998; Sequence No. 0043). The written response was received 02 February 2022 stating, "Based on our review of your use-

related risk analysis (URRA) and justification, we agree that a human factor (b) (4) (HF) validation study does not need to be conducted for licensure”.

Reviewer’s Overall Assessment and Recommendations: The acceptability of the applicant’s rationale that no further HF studies are needed was assessed under the associated IND. Assessment of clinical data as a source of design validation is deferred to the clinical review team.

V. Biocompatibility

Biocompatibility information is provided in Section 1.8.3 of Module 3.2.R Medical Device US. The Applicant is leveraging some information from the supplier, as they state, “The patient contacting surfaces, i.e. fluid path components, are verified based on manufacturers’ information/certificate of conformance and will also be verified for compatibility via extractables and leachables testing.” Notably, Section 1.2.4.2 in Module 3.2.P.2.4 Container Closure, regarding extractables and leachables (E/L) information, states (emphasis added by reviewer) “The rubber plunger used for the syringe is made of (b) (4) polymer with a (b) (4)

Per the E/L information in Module 3.2.P.2.4 Container Closure, the sponsor is leveraging extractables information available from the suppliers for initial satisfaction of E/L information requirements for the BLA. They also plan to conduct a product-specific leachables study: “A leachables study has been initiated using CHIKV VLP unlabeled DP syringes [from PPQ batch (b) (4) (Batch (b) (4) at (b) (4) and finished drug product (FDP) syringes produced from the same DP batch at (b) (4) The DP and FDP syringes will be stored at 2-8°C for 36 months (end of shelf life) and periodically tested for leachables per (b) (4) DP syringe samples will also be tested in an accelerated leachable study performed at (b) (4)

Reviewer Comment: E/L information is reviewed by CMC. At the Late Cycle internal meeting on November 19, 2024, the CMC reviewer indicated that provided information and proposed study are sufficient for approval. A PMC was drafted to ensure the applicant submits the leachables report once available.

The leveraged information is tabulated in Table 4 of Section 1.8.3 of Module 3.2.R Medical Device US, represented below.

Component	Materials	Supplier/DMF	Conformance	Direct Contact with User/ Vaccine	Biocompatibility Compliance Statement Provided
(b) (4)					

(b) (4)

Module 3.2.R also contains RPT055192 CHIKV-VLP PFS Components - Biocompatibility Summary Report, which was generated by Emergent Biosolutions, who originally developed the PFS. The purpose of the report was “to summarize biocompatibility results obtained from manufacturer statements and biocompatibility testing activities on various components constituting the Chikungunya virus virus-like particles (CHIKV-VLP) (PXVX0317) prefilled syringe (PFS) vaccine.” This report considers biocompatibility based on user contact. Subsequently, all components except the plunger stopper and rubber tip cap were identified as having limited (b) (4) direct contact with intact skin of the user (i.e., healthcare professional administering the vaccine). Emergent concluded that the plunger stopper and tip cap “do not need to satisfy the biocompatibility requirement, DIR-047 as per SPE043361.”

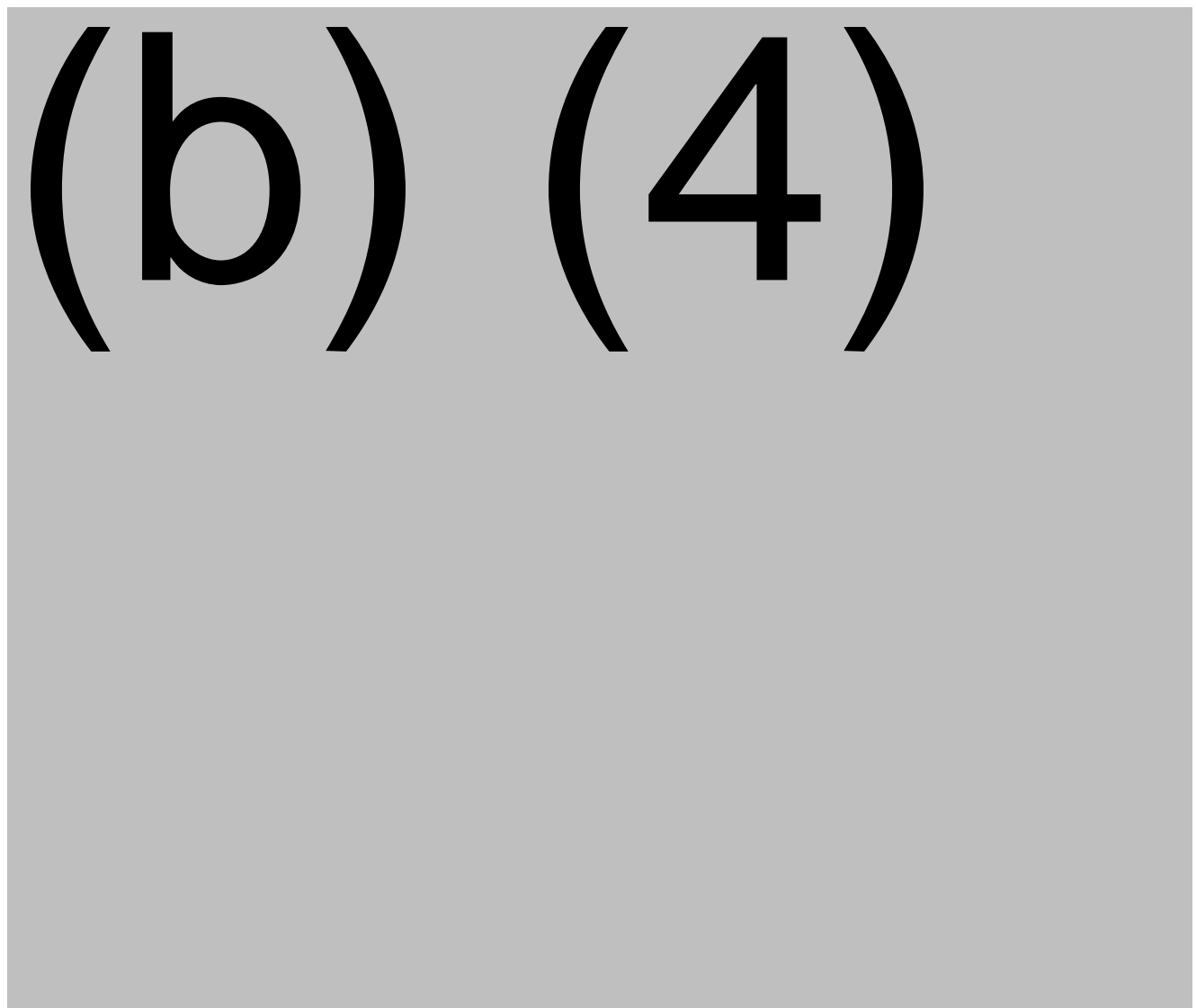
For the other components, “Data to support the biocompatibility test results were either provided by the manufacturer of the pre-fillable syringe components or were generated by an external testing laboratory, (b) (4)

The additional testing by the external laboratory is summarized in Table 5 of Module 3.2.R Medical Device US.

Table 5: Biocompatibility Tests for Finger Flange and Plunger Rod

Component	Biocompatibility Test	Test Results	Reference ^a
Finger Flange	(b)	(4)	
Plunger Rod			

^a References available on request



(b) (4)

Information Request (IR)#40.7

Date Sent: November 21, 2024

Date/Amd/eCTD Sequence Received: December 6, 2024/48/0049

IR Comment: Table 5 in Section 1.8.3 of Module 3.2.R Medical Device US lists biocompatibility testing of the plunger rod and finger flange performed by (b) (4) (b) (4) respectively, and states that the referenced test reports are available upon request. Additionally, you refer to manufacturers' information/certificate of conformance for biocompatibility of the syringe components but did not provide these in the submission. Please provide these test reports and supplier-provided biocompatibility information.

Applicant Response: The (b) (4) comprising all components listed in Table 8, is assembled by (b) (4). A biocompatibility compliance statement for the assembled syringe, issued by (b) (4) is included in this response (BN0085127). The requested biocompatibility testing reports for the plunger rod and finger flange are summarized in Table 9 and included in this response.

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

(b) (4)

Reviewer's Overall Assessment and Recommendations: Biocompatibility information is acceptable.

VI. [Sterility](#)

Section 1.8.4 of Module 3.2.R Medical Device US states "The prefillable syringes are provided as sterile, and ready-to-use with pre-assembled components including the glass barrel, Luer lock adapter, rubber closure, and rigid cap (b) (4) The stoppers are also provided as sterile and ready-to-use form."

Section 1.2.2 of Module 3.2.P.7 states (emphasis added by reviewer), "the syringes comply with the simulated use test according to the current edition of (b) (4)

(b) (4) The **syringes** are (b) (4) assembled, packaged and provided (b) (4) (b) (4) and with a **certificate of conformance** confirming (b) (4) **residuals** (b) (4) which comply with (b) (4) The syringes are provided (b) (4) nested in “Ready to Use” plastic tubs containing (b) (4) with a (b) (4)

Reviewer Comment: The sterilant residual limits in (b) (4) are expressed as maximum average daily doses (e.g., (b) (4) . For a limited exposure device (cumulative sum of single, multiple, or repeated contact is up to (b) (4) the average daily dose of (b) (4) should not exceed (b) (4) and (b) (4) (respectively). The worst-case limit of (b) (4) residuals are (b) (4) (b) (4) per vaccine (b) (4) respectively, which are orders of magnitude below the limits specified in (b) (4) Therefore, the suppliers’ acceptance criteria for (b) (4) are acceptable.

This section also states, “Rubber plunger stoppers are supplied by (b) (4) (b) (4) packaged (b) (4) and (b) (4) per package).”

The supplier specifications and incoming materials specifications are tabulated in Tables 5 through 8 of Module 3.2.P.7, and also include specifications for bacterial endotoxin.

Component	Supplier Spec (Method)	Incoming Material Spec (Method)
(b) (4)		

Reviewer’s Overall Assessment and Recommendations: Review of final product sterility and (b) (4) testing are deferred to CMC and OCBQ. Sterility information of incoming material is acceptable from a device perspective.

VII. Control Strategy

Essential Performance Requirement	Control Strategy Description (e.g., incoming acceptance, in-process control, release testing activities):
(b) (4)	

(b) (4)

Information Request (IR)#40.3

Date Sent: November 21, 2024

Date/Amd/eCTD Sequence Received: December 6, 2024/48/0049

IR Comment: You tabulated supplier specifications and incoming materials specifications for the syringe barrel assembly and the plunger stopper in Tables 5 through 8 of Module 3.2.P.7. You did not provide supplier specifications or incoming materials specifications for the plunger rod or finger flange. Although not product contacting, these are still components of the final finished products. Information is needed to demonstrate how you ensure these components meet your quality requirements. For completeness, please provide supplier specifications or incoming materials specifications for the plunger rod and finger flange.

Applicant Response: Bavarian Nordic (BN) acknowledges that specifications for the plunger rod or finger flange are needed to demonstrate that these components meet the quality requirements. For commercial production BN will purchase the plunger rod and finger flange from the suppliers - (b) (4) (b) (4) respectively. (b) (4) these vendors have been qualified according to the (b) (4) supplier qualification SOP. The plunger rod and finger flange are supplied directly from the vendors to the CMO (b) (4) (b) (4) who performs the final assembly. The CMO is responsible for performing incoming control against their internal specifications for the plunger rod and finger flange. Specifications from (b) (4) containing the vendor specification details relevant for incoming control are included as attachments (Specification of plunger rod for CHIKV VLP vaccine, and Specification of finger flange for CHIKV VLP vaccine), and Section 3.2.P.7 has been updated to include tables for (b) (4) incoming control specifications for the plunger rod and the finder flange, respectively. The tables are included below for convenience.

(b) (4)

Reviewer's Overall Assessment and Recommendations: Control strategy is adequate to ensure final finished product will meet EPRs.

VIII. Packaging, Stability, Shipping

A. Packaging

Section 1.3 of Module 3.2.P.7 states "After final assembly and labeling, one pre-filled syringe is placed in a tray and then packaged in a carton."

Reviewer Comment: See additional descriptions of packaging configuration in shipping validation studies reviewed below in [Section VIII.C](#) of this memo.

B. Stability

Proposed Shelf Life and Storage Conditions: 36 months at 2-8°C

Section 1.8.6 of Module 3.2.R Medical Device US describes aging studies in which the vaccine was "evaluated for device performance at 1.5, 3, 6, and 9 months at

Accelerated aging was conducted at (b) (4) representative of the real time aging of 6, 12, 24, and 36 months", respectively.

Information Request (IR)#40.2

Date/Amd/eCTD Sequence Received: December 6, 2024/48/0049

a. You state that Accelerated aging was conducted at (b) (4) for 1.5, 3, 6, and 9 months, representative of the real time aging at 2 - 8°C of 6, 12, 24, and 36 months, respectively. However, you did not discuss how the representative aging duration was calculated for the accelerated aging study. To confirm the validity of the stated equivalent real time aging durations, please explain how the accelerating aging durations were calculated (e.g., per (b) (4))

b. You did not state what lots/batches were used to conduct the aging studies. Please identify the batches/lots that were used in these stability studies. Please also clarify whether this data overlaps with the stability data provided in Module 3.2.P.8.

Applicant Response:

a. The accelerating aging durations were calculated using the (b) (4) per (b) (4). The variables used to calculate the (b) (4) (b) (4)

The accelerated aging times are calculated per (b) (4) through the use of the (b) (4) (b) (4) Table 4 summarizes the simulated real time shelf-life and actual testing time points for accelerated aging conditions. Values in Table 4 are calculated using an (b) (4)

(b) (4)

b. CHIKV VLP FDP batch number (b) (4) was used for the accelerated aging study. This batch was an engineering run that was representative of the Phase 3 clinical trial material (CTM) manufacturing process. A developmental stability study was performed to (b) (4)-months using CHIKV VLP FDP batch (b) (4). Results of this study are provided in Appendix 1. The stability profile of the batch is representative of the Phase 3 CTM batches presented in Section 3.2.P.8.1.

Reviewer Comments: Response to part a is acceptable. (b) (4) is an FDA-recognized consensus standard.

Regarding part b, this batch was not included in the manufacturing process data reviewed elsewhere in this memo. However, the Applicant did provide a comparability assessment for manufacturing changes implemented between Phase 3 and commercial. The Phase 3 and commercial product use the same container closure and fill volume. Additionally, as Applicant states in the response, the batch (b) (4) stability is representative of the Phase 3 CTM batches presented in Section 3.2.P.8.1. Therefore, there is no overlap with the other data reviewed in this memo, and the data is applicable to the commercial product.

The evaluations after accelerated and real time aging included those listed in Table 3 of Section 1.8.2, which included EPRs (deliverable volume (b) (4) 0.8 mL), (b) (4) (b) (4). Table 7 reports that all samples met acceptance criteria.

Stability information is also provided in Module 3.2.P.8. The table below contains information on DP batches placed on stability, excerpted from Table 5 in Module 3.2.P.8.1 and Table 2 of Module 3.2.P.8.3 Stability Data.

DP Batch	DP DOM	Storage Condition (Planned Duration - Status)	Last available timepoint	Manufactured for / Clinical Use
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(b) (4)	5°C Long-term (b) (4) storage) (36 months - Completed) 5°C Long-term (b) (4) storage) (36 months - Completed) (b) (4) Accelerated (b) (4) storage) (3 months - Completed) (b) (4) Accelerated (b) (4) storage) (3 months - Completed)	36 months 36 months 3 months ^c 3 months ^c	Phase 3 Supporting information
	5°C Long-term (b) (4) storage) (b) (4) months - Ongoing) ^a 5°C Long-term (b) (4) storage) (36 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	36 months 36 months 6 months 6 months	Phase 3 Supporting information
	5°C Long-term (b) (4) storage) (b) (4) months - ongoing) ^a 5°C Long-term (b) (4) storage) (b) (4) months - Completed) ^a (b) (4) Accelerated (b) (4) storage) (6 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	36 months 36 months 6 months 6 months	Phase 3 (b) (4)
	5°C Long-term (b) (4) storage) (b) (4) months - ongoing) ^a 5°C Long-term (b) (4) storage) (b) (4) months - Completed) ^a (b) (4) Accelerated (b) (4) storage) (6 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	36 months 36 months 6 months 6 months	Phase 3 (b) (4)
	5°C Long-term (b) (4) storage) (b) (4) months - ongoing) ^a 5°C Long-term (b) (4) storage) (b) (4) months - Completed) ^a (b) (4) Accelerated (b) (4) storage) (6 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	36 months 36 months 6 months 6 months	Phase 3 (b) (4)
	5°C Long-term (b) (4) storage) (b) (4) months - ongoing) ^a 5°C Long-term (b) (4) storage) (b) (4) months - Completed) ^a (b) (4) Accelerated (b) (4) storage) (6 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	36 months 36 months 6 months 6 months	Phase 3 (b) (4)
	5°C Long-term (b) (4) storage) (b) (4) months - ongoing) ^a 5°C Long-term (b) (4) storage) (b) (4) months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	36 months 36 months 6 months 6 months	Phase 3 Supporting information
	5°C Long-term (b) (4) storage) (b) (4) months - ongoing) ^a 5°C Long-term (b) (4) storage) (b) (4) months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	24 months 24 months 6 months	Phase 3 Supporting information

(b) (4)	(b) (4) months - Completed) ^a (b) (4) Accelerated (b) (4) storage) (6 months - Completed) (b) (4) Accelerated (b) (4) storage) (6 months - Completed)	6 months	
	5°C Long-term (b) (4) storage) (b) (4) months - Ongoing) ^b (b) (4) Accelerated (b) (4) storage) (6 months - Ongoing)	6 months 6 months	Engineering Run Cumulative hold Photostability Supporting information
	5°C Long-term (b) (4) storage) (b) (4) months - Ongoing) ^b (b) (4) Accelerated (b) (4) storage) (6 months - Ongoing)	6 months 6 months	PPQ
	5°C Long-term (b) (4) storage) (b) (4) months - Ongoing) ^b (b) (4) Accelerated (b) (4) storage) (6 months - Ongoing)	6 months 6 months	PPQ Temperature cycling studies
	5°C Long-term (b) (4) storage) (b) (4) months - Ongoing) ^b (b) (4) Accelerated (b) (4) storage) (6 months - Ongoing)	6 months 6 months	PPQ

(b) (4) month time point optional based on availability of samples

(b) (4) month time point optional based on availability of samples.

^c Scheduled for 6 months but due to shortage of samples the study was terminated after the 3-month time point.

The device-relevant testing schedule information below is taken from Table 6 and Table 7 in Module 3.2.P.8.1.

Long-term Storage Stability Design for DP Batches (2–8 °C)

- Container closure integrity testing (CCIT) by (b) (4)
 - 0, 12, 24 months
- Syringe Functionality: (b) (4)
 - 0, 12, 24, 36, (b) (4) months

Accelerated Storage Stability Design for DP Batches (b) (4)

- CCIT by (b) (4)
 - 0, 30 days, 6 months
- Syringe Functionality: (b) (4)
 - 0, 30 days, 6 months

Per Table 8 in Module 3.2.P.8.1, the clinical trial material (CTM) batches acceptance criteria for CCIT (b) (4) and syringe functionality (b) (4) are “Meet the

requirement of (b) (4) method - pass” and (b) (4) respectively. The PPQ acceptance criteria is “Pass” and (b) (4) respectively.

Per Section 3.2.10 through 3.2.12 in Module 3.2.P.8.1 and the corresponding granular data in Module 3.2.P.8.3, “no changes have been observed in syringe functionality or CCI at long-term or accelerated conditions for either phase 3 CTM or PPQ batches.”

Regarding FDP, the table below contains information on batches placed on stability, excerpted from Table 9 in Module 3.2.P.8.1 and Table 3 of Module 3.2.P.8.3 Stability Data.

FDP Batch	FDP DOM	Storage Condition (Planned Duration - Status)	Last available timepoint	Manufactured for / Clinical Use
(b) (4)	21-Jan-2021	5°C Long-term (b) (4) storage) (b) (4) months – Ongoing)	36 months	Phase 3 (b) (4)
	06-Apr-2021	5°C Long-term ((b) (4) storage) (b) (4) months – Ongoing)	36 months	Phase 3 (b) (4)
	17-May-2021	5°C Long-term ((b) (4) storage) (b) (4) months – Ongoing)	36 months	Phase 3 (b) (4)
	22-Apr-2024	5°C Long-term (b) (4) storage) (b) (4) months – Ongoing)	3 months	PPQ
	22-Apr-2024	5°C Long-term (b) (4) storage) (b) (4) months – Ongoing)	3 months	PPQ
	22-Apr-2024	5°C Long-term (b) (4) storage) (b) (4) months – Ongoing)	3 months	PPQ

The device-relevant schedule information below is taken from Table 10 and Table 11 in Module 3.2.P.8.1.

Long-term Stability Design for Phase 3 FDP CTM Batches

- Container Content
 - 0, 6, 12, 18, 24, 36, (b) (4) months
- Container closure integrity testing (CCIT) by (b) (4)
 - 12, 24, 36, (b) (4) months

Long-term Stability Design for FDP PPQ Batches

- Container Content
 - 0, 3, 6, 9, 12, 18, 24, 36, (b) (4) months
- Container closure integrity testing (CCIT) by (b) (4)
 - 0, 12, 24 months
- Syringe Functionality: (b) (4)
 - 0, 3, 12, 24, 36, (b) (4) months

Per Table 12 in Module 3.2.P.8.1, the container content (b) (4) and CCI (b) (4) acceptance criteria are (b) (4) 0.8 mL and “Meet the requirement of (b) (4) (b) (4) method - pass” or “Pass”, respectively, for Phase 3 FDP and PPQ FDP batches. The (b) (4) acceptance criteria are (b) (4)

(b) (4) respectively, for FDP PPQ batches. For commercial stability, these specifications will be monitored on DP rather than FDP.

Section 4.3 of Module 3.2.P.8.1 states “All tested stability parameters for the CHIKV VLP FDP have met their applicable specifications and remained stable over the time periods tested for long-term storage conditions. The currently available data for the phase 3 CTM FDP supports the proposed commercial shelf-life of 36 months from the date of DP manufacture.”

Module 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment states “A post-approval stability study for (b) (4) of both the chikungunya virus virus-like particle (CHIKV VLP) (b) (4) and CHIKV VLP drug product (DP) will be performed (b) (4) at long-term conditions (2 - 8°C)... All currently ongoing stability studies described in Section 3.2.P.8.1 will be continued through the end of the studies. All stability data will be provided, as applicable. In case of confirmed stability out of specification (OOS), the relevant competent authority will be notified. The notification will also include any decision to withdraw from the market based on the safety and efficacy issues associated with the OOS.”

Drug Product Post-Approval Stability Protocol (device relevant information from Table 2 in Module 3.2.P.8.2)

- Container closure integrity testing (CCIT) by (b) (4)
 - 0, 12, 24 months
- Syringe Functionality: (b) (4)
 - 0, 12, 24, 36, (b) (4) (optional), (b) (4) (optional) months

C. Shipping

Section 1.10 of Module 3.2.R Medical Device US states (emphasis added by reviewer) “packaging is evaluated by DIR-42 (b) (4) or DIR-43 (b) (4) or both, for the commercial version of the product. To evaluate the commercial version of the product’s packaging shipping container, the (b) (4) and then **functionally tested per the requirements in Table 3** [of Module 3.2.R Medical Device US, see Appendix 2]. All requirements met their acceptance criteria (b) (4) conditioning. **The CHIKV VLP FDP shipping validation studies are described in Section 3.2.P.3.5.**”

DP (i.e., filled and stoppered PFS, prior to assembly, labeling, and final packaging) **shipping validation studies** are described in Section 2.5.2 of Module 3.2.P.3.5.

Packaging Configuration: (b) (4)

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

(b) (4)

Information Request (IR)#40.1a

Date Sent: November 21, 2024

Date/Amd/eCTD Sequence Received: December 6, 2024/48/0049

IR Comment: In Section 2.5 of Module 3.2.P.3.5, you describe shipping validation studies conducted to demonstrate that drug product (DP) shipping from (b) (4) to (b) (4) and finished drug product (FDP) shipping from (b) (4) to finished product distributors do not adversely affect package integrity, product integrity, syringe functionality, or drug product quality. Please address the following:

- a. In Table 39 in Section 2.5.3, the results column for the (b) (4) design input requirement (i.e., “The PFS average (b) (4) shall be (b) (4) when measured @ (b) (4) states “refer to Section 10.5 for details”. However, there is no Section 10.5 in Module 3.2.P.3.5. To fully understand the reported results, please clarify what this statement refers to and provide any information it was intended to contain, if necessary.
- b. ...
- c. ...

Applicant Response: The reference to “Section 10.5 for details” is a typographical error. This reference was inadvertently copied over from the table in the original source report. Section 10.5 in the original report outlines the data analysis conducted for (b) (4) testing which is aligned with the test method description in Section 3.2.P.5.2. The wording has been deleted from Table 39 in Section 3.2.P.3.5 provided with this response.

Reviewer Comments: *Response is acceptable.*

Study 2: CHIKV VLP PFS FDP simulated shipping study

“Conditioned FDP PFS from the second (b) (4) shipping container described in Study 1 were tested at (b) (4) for product quality.” The results are listed in Table 41. Delivery volume met acceptance criteria (b) (4) 0.8 mL) and remained unchanged from pre- to post-shipping simulation (b) (4)

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

(b) (4)

IX. Comparability Protocols

None submitted.

X. Quality Management System

Section 1.8.1 of Module 3.2.R Regional Information – Medical Device states “The development of the PFS originated within Emergent BioSolutions’s 21 CFR Part 4 and

the MDR Article 10, 9 compliant quality system. This has now transitioned to Bavarian Nordic's quality system which has implemented a streamlined quality system, with an overarching structure compliant with 21 CFR 210 and 211 while integrating the applicable sections of 21 CFR 820. In accordance with 21 CFR art 4.4 the following provisions are applicable to CHIKV VLP Vaccine PFS:

- 21 CFR 820.20 Management Responsibility
- 21 CFR 820.30 Design Controls
- 21 CFR 820.50 Purchasing Controls
- 21 CFR 820.100 Corrective and Preventative Action

21 CFR 820.170, Installation and 21 CFR 820.200 Servicing are not applicable to this product, as it is single use and will be disposed of upon completion of administration."

Device GMP Requirement	Responsible Firm(s):	Summary
21 CFR 820.20 Management Responsibility	Bavarian Nordic	Deferred to OCBQ/DMPQ review.
21 CFR 820.30 Design Controls	Bavarian Nordic	Section 1.8.1.1 of Module 3.2.R Medical Device US states "The development of the PFS has been done in accordance with design control requirements." The summary includes a high-level description of product development plan, risk management plan, identifying user needs and design inputs, design outputs, verification, and validation. Any additional assessment of compliance deferred to inspection.
21 CFR 820.50 Purchasing Controls	Bavarian Nordic	Section 1.8.1.3 of Module 3.2.R Medical Device US states "All Bavarian Nordic suppliers undergo a supplier evaluation in accordance with internal Standard Operating Procedures (SOPs) prior to inclusion on the approved supplier list. Responsibility for the qualification and management of suppliers for the PFS device components reside within the Bavarian Nordic quality group SOPs. Suppliers are re-evaluated on a routine basis, in accordance with internal SOPs." Any additional assessment of compliance deferred to inspection.
21 CFR 820.100 Corrective and Preventive Actions	Bavarian Nordic	Deferred to OCBQ/DMPQ review.

Device GMP Requirement	Responsible Firm(s):	Summary
21 CFR 820.170 Installation	N/A	N/A
21 CFR 820.200 Servicing	N/A	N/A

Reviewer's Overall Assessment and Recommendations: Quality system information is acceptable.

XI. [Appendices](#)

A. Appendix 1 – Analytical Methods and Validation

Reviewer Comment: Review of the analytical method and validation of container closure integrity testing is deferred to DMPQ.

i. Container Content

Information on the analytical methods provided in Module 3.2.P.5.2 Control of Drug Product, analytical Procedures is excerpted below:

(b) (4)

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