

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA 125777/0

Chikungunya Drug Product Lyophilized, Powder for Solution for Injection/ IXCHIQ

Viviana Ramirez, Reviewer, MRB2/DMPQ

1. BLA#: STN 125777/0**2. APPLICANT NAME AND LICENSE NUMBER**

Valneva Austria GmbH and 2309

3. PRODUCT NAME/PRODUCT TYPEProper Name: **Chikungunya Vaccine, Live-Attenuated Vaccine**Proprietary Name: **IXCHIQ****4. GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Pharmacological category: **Vaccine**
- b. Dosage form: **Powder and solvent for reconstitution**
- c. Strength/Potency: **$\geq 3.0 \log_{10}$ TCID₅₀/0.5ml**
- d. Route of administration: **Intramuscular injection**
- e. Indication(s): **Active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and above**

5. MAJOR MILESTONES

- Application receipt date: September 9, 2022
- First Committee Meeting: January 11, 2023
- Filing Meeting: February 2, 2023
- Filing Action: February 20, 2023
- Mid-Cycle Meeting (Internal): April 4, 2023
- Mid-Cycle Communication: April 17, 2023
- Internal Late Cycle Meeting: June 6, 2023
- Major Amendment: August 11, 2023
- Action Due Date (ADD): August 22, 2023
- Revised ADD: October 27, 2023

6. DMPQ CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Viviana Ramirez, OCBQ/DMPQ/MRB2	DS/Drug product

7. INTER-CENTER CONSULTS REQUESTED

No inter-center consults were requested.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments
08/17/2022	STN 125777/0 (eCTD 0000)	Original BLA submission including sections in modules 1, 2 and 4
09/22/2022	STN 125777/0 (eCTD 0001)	Original BLA submission including sections in modules 1 and 4
10/28/2022	STN 125777/0 (eCTD 0002)	Original BLA submission including sections 1, 2 and 3
01/20/2023	Amendment STN 125777/0.05 (eCTD 0005) (response to information request (IR) #4)	Included information regarding stability
01/25/2023	Amendment STN 125777/0.06 (eCTD 0006) (response to IR #6)	Included information on computer systems for critical manufacturing processes
02/06/2023	Amendment STN 125777/0.08 (eCTD 0008) (response to IR #9)	Information on facilities; clarification of manufacturing and testing activities
05/15/2023	Amendment STN 125777/0.50 (eCTD 0049) (response to IR #42)	Information on shipping and device.
06/28/2023	Amendment STN 125782/0.56 (eCTD 0055) (response to IR #55)	Information related to shipping, including protocols
07/05/2023	Amendment STN 125777/0.60 (eCTD 0059) (response to IR# 55)	Information related to shipping, including reports
07/06/2023	Amendment STN 125777/0.61 (eCTD 0060) (response to IR #59)	Information on facility
07/18/2023	Amendment STN 125777/0.66 (eCTD 0065) (response to IR# 55)	Information related to shipping, including protocols and reports VIE-VR-0233 23-1006113-TP-1-V1

Date Received	Submission	Comments
07/24/2023	Amendment STN 125777/0.70 (eCTD 0068) (response to IR# 69 and 70)	The process validation report for labelling and packaging validation activities performed at (b) (4) will be provided by July 31, 2023.
07/31/2023	Amendment STN 125777/0.74 (eCTD 0072) (response to IR# 60, 61 and 64)	Labelling and Packaging Validation from (b) (4)

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Valneva Austria GmbH (Valneva) submitted BLA STN 125777/0 as a rolling BLA submission for the licensure of Chikungunya Vaccine, Live-Attenuated Vaccine (IXCHIQ), intended for active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and above. CBER/DMPQ reviewed and evaluated the drug substance (DS) and drug product (DP) manufacturing processes and facilities proposed for use in the manufacture of IXCHIQ. Information reviewed, evaluated, and documented in this memo includes data to validate and support the consistency of the manufacturing process and product quality; facility information which includes utilities, cross-contamination prevention measures, and maintenance of controlled environments; and equipment for use in the manufacturing (all product-contact equipment used in DS and DP manufacturing are single-use).

The DS manufacturing site, Valneva Scotland Ltd., completed validation and qualification activities that included but were not limited to process, Container Closure Integrity Testing (CCIT) of (b) (4), environmental monitoring performance testing, and qualification of the Biological Safety Cabinets (BSCs) including validation of the disinfection/decontamination process. The facility is designed for the prevention and control of contamination and cross-contamination with many engineering and procedural controls in place, including single-use product-contact components. The overall control strategy supports sterility assurance and consistency of manufacturing.

The drug product manufacturing site, (b) (4), completed validation and qualification activities that included but were not limited to process, aseptic process media simulation studies, container closure integrity testing, environmental monitoring performance testing, and qualification of the isolator, including validation of the disinfection/decontamination process, and the (b) (4) vial washer and depyrogenation tunnel qualifications. The facility is designed for the prevention and control of contamination and cross-contamination with many engineering and procedural controls in place, including single-use product-contact components and isolator technology. The overall control strategy supports sterility assurance and consistency of manufacturing. The information submitted in the application is acceptable and was confirmed during the review of (b) (3) (A), (b) (4)

The water for injection Pre-Filled Syringe (PFS) manufacturing site, (b) (4) completed validation and qualification activities that included but were not limited to aseptic process media simulation studies, container closure (syringe barrel, tamper-evident closure and a rubber stopper) integrity testing, environmental monitoring performance testing, and qualification of the restricted access barrier system (RABS), including validation of the disinfection process, and primary container washer, autoclave and depyrogenation tunnel qualifications. The facility is designed for the prevention and control of contamination and cross-contamination with many engineering and procedural controls in place, including single-use product-contact components and RABS technology. The overall control strategy supports sterility assurance and consistency of manufacturing.

The inspection waivers for the facilities were based on the evaluations of the facilities' inspection compliance histories. The inspection waivers are documented in a separate inspection waiver memo dated April 26, 2023, which is uploaded to CBER Connect under BLA STN 125777/0.

This submission was granted priority review with 8-month review cycle. On August 11, 2023 a Major Amendment was issued. The ADD was revised from August 22, 2023 to October 27, 2023.

B. Recommendation

I. APPROVAL

Approval is recommended based on the review of the information submitted to BLA 125777/0 including information provided in the corresponding amendments and the inspectional compliance history evaluations.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Viviana Matta, CMC / Facility Reviewer, OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo, Branch Chief, CBER/OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw, Director, CBER/OCBQ/DMPQ	Concur	

Table of Contents

3.2.S DS.....	9
3.2.S.2 Manufacture	9
3.2.S.2.1 Manufacturer(s).....	9
3.2.S.2.2 Description of Manufacturing Process	9
3.2.S.2.3 Control of Materials	11
3.2.S.2.4 Controls of Critical Steps and Intermediates.....	13
3.2.S.2.5 Process Validation and/or Evaluation.....	13
3.2.S.4 Control of DS.....	15
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s).....	Error!
Bookmark not defined.	
3.2.S.4.4 Batch Analyses	16
3.2.S.6 Container Closure System	16
3.2.S.7 Stability.....	16
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data	16
3.2.P DRUG PRODUCT: Lyophilized IXCHIQ Vials	17
3.2.P.1 Description and Composition of the Drug Product.....	17
3.2.P.2.4 Container Closure System	17
3.2.P.2.5 Microbiological Attributes	17
3.2.P.3 Manufacture	18
3.2.P.3.1 Manufacturer(s).....	18
3.2.P.3.3 Description of Manufacturing Process	18
3.2.P.3.4 Controls of Critical Steps and Intermediates.....	22
3.2.P.3.5 Process Validation and/or Evaluation.....	Error! Bookmark not defined.
3.2.P.5 Control of Drug Product.....	33
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	33
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.....	34
3.2.P.5.4 Batch Analyses	34
3.2.P.7 Container Closure System	34
3.2.P.8 Stability.....	36
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	36
3.2.P DRUG PRODUCT: WFI Pre-Filled Syringe.....	37
3.2.P.1 Description and Composition of the Drug Product.....	37
3.2.P.2.4 Container Closure System	38
3.2.P.2.5 Microbiological Attributes	38
3.2.P.3 Manufacture	38
3.2.P.3.1 Manufacturer(s).....	38
3.2.P.3.3 Description of Manufacturing Process	38
3.2.P.3.4 Controls of Critical Steps and Intermediates.....	40
3.2.P.3.5 Process Validation and/or Evaluation.....	40
3.2.P.5 Control of Drug Product.....	52
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	52
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.....	53
3.2.P.5.4 Batch Analyses	53

3.2.P.7 Container Closure System 53
3.2.P.8 Stability 56
 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data 56
3.2.A APPENDICES **Error! Bookmark not defined.**
3.2.R Regional Information (USA)..... **Error! Bookmark not defined.**

Module 3

3.2.S Drug Substance

The active ingredient in the DS of the Chikungunya vaccine is a live-attenuated chikungunya virus CHIKV ($\Delta 5nsP3$) based on the (b) (4) genotype of the (b) (4) lineage LR2006-OPY1. It comprises a large deletion of (b) (4) amino acids in the (b) (4) part of the nsP3 gene that encodes the non-structural protein nsP3 part of the replicase complex, leading to a reduced replication capability of the virus *in vivo*. The virus is propagated on Vero cells and purified by centrifugation, ultrafiltration, batch chromatography, and sucrose gradient centrifugation. The Chikungunya vaccine contains no adjuvant and is intended to induce a rapid development of a protective antibody titre.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

See section 3.2.A.1 for a complete list of DS manufacturers.

(b) (4)

■

[Redacted]

[Redacted]

[Redacted]

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

(b) (4)



3.2.P DRUG PRODUCT: Lyophilized IXCHIQ Vials

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

The IXCHIQ vaccine candidate kit contains one single-use (b) (4) vial with the lyophilized DP (b) (4) TCID₅₀) and one prefilled syringe of solvent containing 0.5 mL sterile WFI for reconstitution and administration of the reconstituted vaccine. The drug product is formulated with 0.313 mg di-potassium hydrogen phosphate, potassium di-hydrogen phosphate 0.098 mg, trisodium citrate dihydrate 3.68 mg, sucrose 25 mg, magnesium chloride hexahydrate 0.51 mg, D-sorbitol 2.5 mg, L-methionine 0.75 mg, and recombinant human albumin (rHA) 0.05mg (equals 0.01%). The container closure system used for the lyophilized DP consists of Type (b) (4) glass (b) (4) vial closed with freeze-dry bromobutyl injection stopper (13mm) and 13 mm flip-off cap.

When formulating the final DP bulk vaccine, a target formulation titer (b) (4) than the release specification has been adopted to account for any potential loss of viral activity by surface adsorption during DP bulk preparation, sterile filtration, filling and lyophilization, as well as potential loss of viral activity during storage of the lyophilized DP. There is no fill overage.

3.2.P.2.4 Container Closure System

Refer to section 3.2.P.7 Container Closure System for the primary container closure system description, specifications, and its qualification (per DMPQ purview).

3.2.P.2.5 Microbiological Attributes

The IXCHIQ drug product is manufactured as a sterile DP by aseptic processing, and supplied as preservative-free, single-use vials. The DS is manufactured using a bioburden-controlled process. (b) (4) to the DP compounding process. As part of the aseptic filling process, DP solution is filtered through (b) (4) filters. DP is aseptically filled and lyophilized using a validated process, and all product-contact components are either received sterile or sterilized during validated process. The DP

formulation buffer is tested for (b) (4) for sterility and bacterial endotoxins. A (b) (4) bioburden test (acceptance criteria: (b) (4)) is performed on the formulated DP bulk. Following sterile filtration, a test for sterility is performed.

DP is subject to sterility and endotoxin testing as part of the release process, with acceptance criteria of no growth and (b) (4)/0.5mL, respectively. Assurance of container closure system integrity during shipping was established by the shipping validation study. The container closure integrity of the primary packaging systems was demonstrated by (b) (4)

(b) (4) A test for (b) (4) DP lot after reconstitution as a QC release test.

Reviewer's Assessment: *The microbial attributes and control strategy appear acceptable. The bioburden-controlled DS manufacturing process is reviewed in Section 3.2.S.2.4. The sterile filtration steps for the DP are reviewed in Sections 3.2.P.3.3 and 3.2.P.3.4. DP aseptic filling and lyophilization process validation, as well as product-contact material sterilization process validation are reviewed in Section 3.2.P.3.5. Container closure integrity testing validation is reviewed in Sections 3.2.P.5.3 and 3.2.P.7.*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities

3.2.P.3.3 Description of Manufacturing Process

The IXCHIQ DP manufacturing process is performed at (b) (4) facility in (b) (4) in Buildings (b) (4) and include the following steps.

(b) (4)

(b) (4)

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

Visual inspection: The product vials are subject to a 100 % visual inspection after a (b) (4) of storage time at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ (action limit: total reject rate: (b) (4)) to also detect leakage due to possibly damaged glass vials or cake collapses. Additionally, an acceptable quality limit (AQL) inspection is performed for (b) (4). After visual inspection, vials are packed into storage boxes before being sampled for release testing.

Storage: The drug product vials are stored at $5^{\circ} \pm 3^{\circ}\text{C}$.

Labeling and packaging: DP lyophilized is transported from (b) (4) to receiving sites for storage and/or assembly of the Final Product (commercial kit) located in (b) (4) in qualified and calibrated active temperature-controlled vehicles maintained at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

(b) (4) will be responsible for syringe labelling and assembly (assemble plunger rod and backstop to the sterile WFI PFS vial labelling and kitting). At time of approval of the process validation report there were 2 outstanding CAPAs, both with due dates for 31 October 2023:

- CAR QE-014160: Software update by the supplier to enable the communication for batch specific data between (b) (4) and the printer.
- CAR QE-014382: Follow up on flagging labels on sterile water for injection syringes. PV runs executed according to Temporary Change QE-014333.

After completion of action items for CAPA (CAR QE-014382) the system in production area (b) (4) can be released for commercial production of sterile water for injection syringes.

Long-term storage: The final drug product vials are stored at $5^{\circ} \pm 3^{\circ}\text{C}$ at (b) (4)

Nomenclature: The batch number is a 7-digit number XXXMMYY, as follows:

- (b) (4)

Batch size: DP Bulk Batch size is a maximum of (b) (4). DP Lyophilized (Final Lot) size is a maximum batch size of (b) (4) vials.

Reviewer's Assessment: Adequate information is provided for the DP process description. Description and assessment of controls associated with critical steps operating and performance parameters, in-process controls and hold-times are provided in sections 3.2.P.3.4 Controls of Critical Steps and Intermediates, and 3.2.P.3.5 Process Validation. Labeling and packaging operations have been qualified.

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

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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)

DP specifications under DMPQ purview were previously reviewed in section 3.2.P.2.5 Microbiology Attributes.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

CCIT and its method validation is reviewed in Section 3.2.P.7 Container Closure System. Evaluation of other analytical methods is deferred to OVRR and DBSQC reviewers.

3.2.P.5.4 Batch Analyses

Batch analyses results are provided for (b) (4) lots that were manufactured from June 18, 2020, to July 10, 2021, with the commercial process. These batches cover clinical lots (0030620 and 0050721), (b) (4) DP process validation batches including the (b) (4) DP PPQ lots (b) (4). Batch sizes range from (b) (4) vials.

The batch analyses testing under DMPQ purview included sterility and endotoxin tests and the acceptance criteria are no growth and (b) (4)/0.5 mL, respectively. All batches met the sterility acceptance criteria, and all batches met the endotoxin acceptance criteria with the highest endotoxin level at (b) (4) /0.5mL.

Reviewer's Assessment: Lots included in the batch analyses appear suitable, including the three consecutive DP validation runs. There were no deviations for the batch testing under DMPQ purview.

3.2.P.7 Container Closure System

The container closure system for the lyophilized DP consists of (b) (4) Type (b) (4) borosilicate glass vial (b) (4) vial), a 13 mm bromobutyl rubber stopper and a 13 mm aluminum cap with polypropylene closure. The components of the container closure system are listed in following table:

IXCHIQ DP Container Closure Components

Component	Description	Manufacturer	Standards
Vial	(b) (4) injection vial (b) (4) Type (b) (4) clear borosilicate glass, 13 mm neck	(b) (4)	(b) (4)
Stopper	13 mm stopper of (b) (4) (Bromobutyl compound free from natural rubber and natural rubber	(b) (4)	(b) (4)

Component	Description	Manufacturer	Standards
	latex, not containing (b) (4)	Product No: (b) (4)	
Cap	13 mm Aluminum caps with polypropylene closure (flip-off), color silver-blue.	(b) (4) Product No: (b) (4)	(b) (4)

The components of the container closure system are released against specifications based on the Certificate of Analysis (CoA) provided by the manufacturer such as material/identify and endotoxin (only for stoppers and acceptance criteria is (b) (4)). Before use, the vials are (b) (4).

. Vial depyrogenation/sterilization, and stopper and capper sterilization qualification are reviewed in Section 3.2.P.3.5 Process Validation and/or Evaluation.

The primary packaging system (b) (4) vial + 13 mm lyophilization stopper + 13 mm Flip off cap) was proposed by (b) (4), at the beginning of the project during initial transfer, since this primary packaging combination was routinely used as "standard" for lyophilized products on (b) (4) filling line (b) (4) in Building (b) (4) and therefore prior knowledge (including successful container closure integrity results from other products) with this primary packaging configuration was already available. This combination was also considered acceptable for the product based on its composition.

The secondary packaging for commercial supply is intended to comprise of the following:

- Components: 1 x labelled vial containing Drug Product Lyophilized and 1 x labelled sWFI Pre-Filled Syringe, assembled with plunger rod and backstop
- Secondary Components: 1 x tray insert, 1 x labelled folding box and 1 x leaflet

CCIT by (b) (4)

Lyophilized products like IXCHIQ DP are closed with a container closure system using a (b) (4). Therefore, a defective vial with (b) (4) could be detected by measuring the (b) (4) level. Acceptance criterion is defined as individual values (b) (4) should not deviate by more than (b) (4) from the mean value (b) (4).

(b) (4)

As noted in previous section, capping parameters were validated using container-closure integrity testing (CCIT). CCIT was successfully performed on the (b) (4) PPQ and on (b) (4) clinical lots CTM3 (Lot 2005040029/0030620) and CTM5 (Lot 2106090052/0050721). CCIT was also assessed at the end of shelf-life (after 2 years of storage at the recommended storage temperature), shipment and secondary packaging activities for clinical lot (b) (4) and the (b) (4) PPQ batches. CCIT is evaluated by (b) (4), the calculated limit of detection (b) (4)

All aforementioned batches met acceptance criteria (individual values (b) (4) should not deviate by more than (b) (4) from the mean value (b) (4)). CCIT was also performed on lot (b) (4). All vials tested passed.

Reviewer's Assessment: All lots included in the (b) (4) for container closure integrity testing met acceptance criteria. The IXCHIQ DP container closure system appears to be appropriately validated.

3.2.P.8 Stability

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

Primary stability data consist of long-term data at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ (recommended storage conditions), accelerated data at (b) (4). Stability study design is delineated below:

- Long Term Storage Condition at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$: Sterility is tested at study start with an acceptance criterion of no growth, and endotoxin testing is scheduled for 12, 24, (b) (4) months with an acceptance criterion of (b) (4) EU/mL. Sterility testing is scheduled for 12, 24, (b) (4) months.
- Accelerated Stability Conditions (b) (4): Sterility is tested at study start with an acceptance criterion of no growth, and endotoxin testing is

scheduled for (b) (4) timepoint with an acceptance criterion of (b) (4) EU/mL. Sterility testing is scheduled for (b) (4) timepoint.

- Degradation Stability Conditions (b) (4) Sterility is tested at study start with an acceptance criterion of no growth, and endotoxin testing is scheduled for (b) (4) timepoint with an acceptance criterion of (b) (4) EU/mL. Sterility testing is scheduled for (b) (4) timepoint.

Sterility was confirmed at time 0 of the standard stability study and at time 0 of the cumulative study (b) (4) storage at (b) (4) It was also confirmed at the end of the accelerated study (standard stability study) and at the end of the forced degradation study (both standard study and cumulative study).

The primary stability DP lyophilized lots, when stored at the recommended storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, have remained within specifications for up to (b) (4) months for Lot 2005040029 (used in the Phase 3 Clinical Trial VLA1553-301) and for the (b) (4) Process Performance Qualification Lots, (b) (4). At the accelerated condition of (b) (4) the primary stability DP lyophilized lots remained within specifications for up to 6 months. During the forced degradation study at (b) (4) the primary stability DP lyophilized lots remained within specifications for up to (b) (4) weeks.

CCIT was assessed at the end of shelf-life (after 2 years of storage at the recommended storage temperature), shipment and secondary packaging activities for Clinical Lot 2005040029/0030620 (CTM3) and the (b) (4) PPQ batches.

A 24-month shelf-life is proposed for the lyophilized DP when stored at the recommended storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. This shelf life is supported by the results of the primary stability DP lyophilized lots, the clinical Phase 3 lot, 2005040029, (b) (4). These lots remained within specifications for up to (b) (4) months when stored at the recommended storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

In amendment STN 125777/0.61 (0060), the Valneva agreed to include CCIT at product expiry in their post-approval stability protocol.

Reviewer's Assessment: *The sterility, endotoxin and CCIT testing schedules on the stability study appear acceptable. The testing results support the shelf life of 12 months stored at (b) (4) from DMPQ perspective.*

3.2.P DRUG PRODUCT: WFI Pre-Filled Syringe

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

The solvent is sterile WFI filled in a (b) (4) syringe format. The composition of the sterile WFI prefilled syringe (PFS) is 0.50 mL minimum extractable volume.

The container closure system consists of a siliconized glass barrel, a siliconized plunger, and a closure system (b) (4) composed of a tip cap with a luer lock and a tamper-evident seal.

3.2.P.2.4 Container Closure System

Refer to section 3.2.P.7 Container Closure System for the primary container closure system description, specifications, and its qualification (per DMPQ purview).

3.2.P.2.5 Microbiological Attributes

The sterile WFI is filled in a container closure system comprising a syringe barrel, a (b) (4) tamper-evident closure and a rubber stopper (b) (4) formats with the same stopper and (b) (4) Manufacture of the sterile WFI PFS consists of (b) (4) step. The manufacturing process is controlled by (b) (4) in accordance with (b) (4) To control the microbial attributes at release and during shelf life of the sterile WFI PFS, sterility (no growth) and bacterial endotoxins testing (b) (4) are performed in accordance with (b) (4)

During development, the integrity of the container closure system was validated by conducting container closure integrity (CCI) testing to prevent microbial contamination.

Reviewer's Assessment: *The microbial attributes and control strategy appear acceptable. The sterile filtration steps are reviewed in Sections 3.2.P.3.3 and 3.2.P.3.4. DP aseptic filling and process validation, as well as product-contact material sterilization process validation are reviewed in Section 3.2.P.3.5. Container closure integrity testing validation is reviewed in Sections 3.2.P.5.3 and 3.2.P.7.*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

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

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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)

DP specifications under DMPQ purview are reviewed in section 3.2.P.2.5 Microbiology Attributes.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

CCIT and its method validation are reviewed in Section 3.2.P.7 Container Closure System. Evaluation of other analytical methods is deferred to OVRP and DBSQC reviewers.

3.2.P.5.4 Batch Analyses

Batch analyses results were provided for (b) (4) lots that were manufactured from April 28, 2018, to September 14, 2020, with the commercial process. These (b) (4) batches were part of the (b) (4) that covered the 0.50 mL minimum extractable volume (MEV) in a 1.5 mL syringe format and (b) (4) mL MEV in a (b) (4) mL syringe format. In addition, batch analyses of the (b) (4) PPQ batches manufactured in 2008 were provided.

Under DMPQ purview, the batch analyses testing including sterility and endotoxin tests and the acceptance criteria are no growth and (b) (4), respectively. All batches met the sterility acceptance criteria, and all batches met the endotoxin acceptance criteria.

Reviewer's Assessment: *Lots included in the batch analyses appear acceptable. There were no deviations for the batch testing under DMPQ purview.*

3.2.P.7 Container Closure System

The container closure system comprises a syringe barrel, a (b) (4) tamper-evident closure and a rubber stopper. The following table describes container closure components.

Description of the Container Closure Components

Component	Description	Supplier
Syringes	1.5 mL syringe: Borosilicate glass, type (b) (4) with Luer cone and groove, compliant with (b) (4)	(b) (4)
Rubber stopper	Bromobutyl rubber, type (b) (4) (b) (4) compliant with (b) (4)	(b) (4)
(b) (4)	Consisting of a tip cap, a Luer lock and a tamper-evident seal Product contact part of (b) (4) Tip cap: bromobutyl rubber, (b) (4) compliant with (b) (4)	(b) (4)

The incoming test procedures that the syringes undergo on delivery to (b) (4) include supplier certificate and visual identity. The incoming test procedures that the rubber stoppers undergo on delivery to (b) (4) include supplier certificate, chemical identity (b) (4) and visual inspection.

The (b) (4) closure consists of a tamper-evident seal, a Luer lock and a rubber tip cap. The closure is designed to guarantee the integrity of the prefilled syringe system. Before syringe usage the tamper-evident caps need to be (b) (4)

(b) (4)

Container Closure Integrity Testing

The (b) (4) test for container closure integrity is used to assess the effectiveness of the individual container closure components to prevent any leakage. Verification of the container closure was performed by applying container closure integrity test (b) (4) testing) on units for all manufactured initial validation batches.

Due to identical primary container closure systems, the container closure integrity test was not repeated within the revalidation activities conducted in 2012. Container closure integrity testing is also included in the stability testing program. Refer to Section 3.2.P.8 Stability for a description of the stability program and approach.

For method validation, defects were simulated with (b) (4)

(b) (4) testing was performed on the (b) (4) sterile WFI PFS validation batches manufactured in 2008 “for information only”. (b) (4) testing is not applicable as part of the regular release and stability testing as the syringe is used as a diluent/solvent and not applied to patients. Due to identical primary container closure systems, the (b) (4) testing was not repeated within the requalification activities conducted in 2012.

(b) (4)

(b) (4)

3.2.P.8 Stability

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

The worst-case conditions regarding stability were identified as a MEV of 0.50 mL in the 1.5 mL syringe format and a MEV of (b) (4) mL in the (b) (4) mL syringe format. Therefore, initial stability studies were conducted on (b) (4) validation batches of sterile WFI prefilled syringes (PFS) manufactured at (b) (4) during initial process qualification (PQ) campaign in 2008:

- (b) (4) batches of the 1.5 mL syringe format filled with a MEV of 0.50 mL
- (b) (4) batches of the (b) (4) mL syringe format filled with a MEV of (b) (4) mL

As supportive data, (b) (4) batches of the 1.5 mL syringe format filled with a MEV of (b) (4) mL were manufactured and tested in addition. All (b) (4) listed batches were manufactured according to the defined commercial process and utilized the defined primary packaging materials. The stability samples were stored at the following conditions:

- Long-term 2°C to 8°C / ambient relative humidity (RH) over a period of (b) (4) months
- Long-term (b) (4) over a period of (b) (4) months
- Accelerated (b) (4) over a period of (b) (4) months

The acceptance criteria for microbiological attributes were tested as follows: Bacterial endotoxins (b) (4) at 0, 12, 24, (b) (4) months; and sterility (no growth) at 0, 12, 24, (b) (4) months. In addition, container closure integrity testing (no (b) (4) migration into the interior of the test system) is scheduled at 0, 12, 24, (b) (4) months. The stability studies have been completed and all results available up to (b) (4) months met acceptance criteria for the MEVs of 0.50 mL and (b) (4) mL sterile WFI covering all presentations in between the MEVs evaluated. A shelf-life of (b) (4) months for the sterile WFI PFS when stored at (b) (4) is confirmed with the stability data obtained.

(b) (4) performs stability testing on (b) (4) sterile WFI prefilled syringe (PFS) batch of each 0.50 mL MEV in the 1.5 mL syringe format and (b) (4) mL MEV in the (b) (4) mL syringe format once a (b) (4). The stability program is based on the same worst-case (b) (4) applied for process validation. Thus, the stability studies using the 0.50 mL and (b) (4) mL MEVs are representative of all other volumes covered by the (b) (4). Batches will be randomly selected and placed on stability. The post-approval stability protocol includes testing of samples stored at the long-term 2 to 8°C / (b) (4) storage conditions.

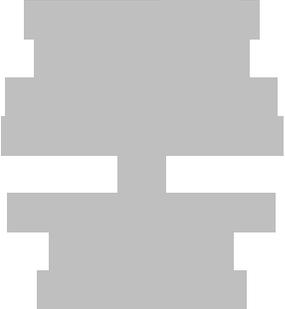
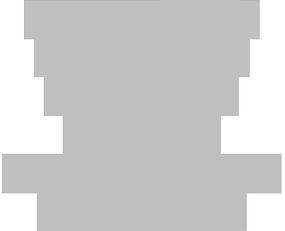
Reviewer’s Assessment: *Provided stability data and stability protocol/commitment are acceptable from DMPQ perspective.*

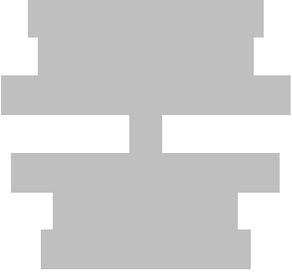
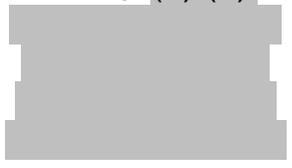
3.2.A APPENDICES

Facilities Table

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: Valneva Scotland Ltd. (subsidiary) Oakbank Park Road Livingston, Scotland UK EH53 0TG FEI#: 3005315117</p> <p>Actions: Manufacture of DS</p>	Waiver	Yes	Yes	<p>2022 Surveillance ORA/OBPO VAI</p>
<p>Facility: (b) (4)</p> <p>FEI#: (b) (4)</p> <p>Actions: Formulation, Filling and Lyophilization of Drug Product</p>	Waiver	Yes	Yes	<p>2019 DMPQ PLI VAI</p> <p>The formulated DP is sterile filtered before filling and the firm provided aseptic fill qualification. The lyophilization process has not been inspected by FDA.</p> <p>Lyophilization process and equipment was evaluated by (b) (3) (A), (b) (4) . Acceptable.</p>

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: Valneva (b) (4)</p> <p>FEI#: (b) (4)</p> <p>Actions: Drug Product Appearance and Bacterial Endotoxin for Release</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>2011 ORA/DFI Limited inspection VAI</p> <p>Quality and laboratory system evaluated by (b) (3) (A), (b) (4)</p> <p>Acceptable.</p>
<p>Facility: (b) (4)</p> <p>FEI#: (b) (4)</p> <p>Actions: Manufacture of sterile water for injection (= solvent) in prefilled syringes, Visual Inspection Quality Control Testing: In-process control and release and/or shelf life testing</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>2023 CDER PLI VAI</p> <p>Filled and stoppered WFI syringes are <i>terminally sterilized</i>. Acceptable.</p>

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: (b) (4)</p>  <p>FEI#: (b) (4)</p> <p>Actions: Quality Control Testing of sterile water for injection (= solvent): In-process control and release and/or shelf-life testing</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>2022 CDER PLI VAI</p>
<p>Facility: (b) (4)</p>  <p>FEI#: (b) (4)</p> <p>Actions: Visual Inspection of sterile water for injection (= solvent) Quality Control Testing of sterile water for injection (= solvent): In-process control and release and/or shelf-life testing</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>2022 CDER PLI VAI</p>

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: (b) (4)  FEI#: (b) (4)</p> <p>Actions: Visual inspection of sterile water for injection (= solvent) Quality Control Testing of sterile water for injection (= solvent): Chemical / physical testing and for shelf-life testing only Storage of sWFI PFS</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>2019 ORA/OBPO Surveillance VAI</p>
<p>Facility: (b) (4)  FEI#: (b) (4)</p> <p>Actions: In-Process Testing DS and Drug Product Release Testing</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>ORA/FOR-MPT 2017 Surveillance VAI 2019 MRA Surveillance NAI</p>

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: (b) (4)</p> <p>FEI#: (b) (4)</p> <p>Actions: In-Process Testing</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	
<p>Facility: (b) (4)</p> <p>FEI#: (b) (4)</p> <p>Actions: Final assembly, primary labeling and packaging</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>2020 PAI CDER NAI</p>
<p>Facility: (b) (4)</p> <p>FEI#: N/A</p> <p>Actions: Storage of DS</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: (b) (4)</p>  <p>FEI#: N/A</p> <p>Actions: Storage of DS and Drug Product and Sterile Water for Injection</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	
<p>Facility: (b) (4)</p>  <p>FEI#: N/A</p> <p>Actions: Storage of DS and Drug Product and Sterile Water for Injection</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	
<p>Facility: (b) (4)</p>  <p>FEI#: N/A</p> <p>Actions: Storage of Drug Product and Sterile Water for Injection</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	

Valneva Scotland Ltd. DS Manufacturing Facility

Facility Design

IXCHIQ DS is manufactured at Valneva Scotland Ltd. located in Scotland UK. The firm is experienced in cell culture, viral amplification, viral harvest, pooled harvest concentration and filtrations. The manufacturing facility building encompasses the (b) (4) Clean Room Suite plus an area to receive incoming goods, within the overall scope of the original building shell. The remainder of the building is occupied by offices, QC labs, an additional fully segregated cleanroom suite, storage, warehousing and utilities. The (b) (4) clean room suite has been built and qualified to be capable of manufacturing large scale (b) (4) or (b) (4) viral vaccines whilst maintaining the required environmental control and quality. The (b) (4) clean room suite is the designated area for the commercial manufacture of the IXCHIQ DS. The (b) (4) clean room suite consists of (b) (4) manufacturing clean rooms, (b) (4) Clean Room (b) (4) Clean Room (b) (4). There is no (b) (4) used and the manufacturing suite for Chikungunya Vaccine is qualified to be capable of manufacturing large scale Containment (b) (4) or Containment (b) (4) vaccines whilst maintaining the required environmental control and quality.

Personnel Flow: To prevent potential contamination, restrictions on access and movement are enforced. Access to the clean rooms is gained (b) (4). Access is restricted by use of a proximity (b) (4) to authorized personnel only. The clean room doors are (b) (4). Personnel flow into and around the (b) (4) Clean Room suite is clearly (b) (4). Once entrance has been made to the (b) (4) Entry to each of the manufacturing clean rooms is through (b) (4) into full clean room clothing.

Material/Waste Flow: Material transfer into the (b) (4) Clean Room suite is clearly (b) (4)

(b) (4)

[Redacted]

[Redacted]

(b) (4)

Reviewer's Assessment: The facility flow descriptions were reviewed and found acceptable. Unidirectional personnel flow appears to be implemented in Grade (b) (4) Grade (b) (4) manufacturing areas. ORA/OBPO conducted an inspection of Valneva Scotland Ltd. facility on September 09, 2023, and the inspection was classified as VAI. No issues were identified.

Prevention of contamination and cross-contamination

The IXCHIQ DS is not required to be sterile, and its manufacturing is a bioburden-controlled process. Prevention of contamination and cross-contamination is ensured by proper facility, equipment, process, and operational controls at the Valneva Scotland Ltd. facility.

The facility maintains area classifications. (b) (4)

Production is (b) (4) to be manufactured in a room. Product changeover and facility cleaning are conducted per established SOPs. Valneva Scotland Ltd. facility relies on single use, sterile, disposable process technology wherever process allows. For non-disposable manufacturing equipment, cleaning considerations include selection of test points to represent worst case testing, use of (b) (4) to effectively evaluate cleaning.

Reviewer's Assessment: The contamination and cross-contamination control features and procedures are reviewed and found acceptable. Facility cleaning and room

changeover procedures were evaluated in the inspection conducted by ORA/OBPO on September 09, 2023, and the inspection was classified as VAI. No issues were noted; procedures appear acceptable.

Facility cleaning and disinfectant effectiveness studies

Cleaning within the (b) (4) clean rooms is carried out by trained staff and the procedures are documented in SOPs. These SOPs detail the cleaning materials to be used, rotation of disinfectants, required frequency of cleaning etc. Facility cleaning is (b) (4)

(b) (4) These are typically areas where the product is exposed to the environment. Product is only exposed within controlled environments such as Class (b) (4)

These areas are cleaned (b) (4)

Additional information regarding disinfectant studies for the (b) (4) (b) (4)

(b) (4) was provided in amendment STN 125777/0.61 (eCTD 0060) received July 6, 2023 in response to an information request. The testing of disinfectants was performed at (b) (4), which is a microbiological contract testing laboratory specializing in testing of disinfectants. Surfaces included in the testing were noted as (b) (4)

The

acceptance criteria that was applied during the efficacy studies performed followed (b) (4) ; for bacteria and yeast (vegetative form) (b) (4) and for bacterial and fungal spores (b) (4). Valneva employs a (b) (4) program to complement each disinfectant for overall elimination of contaminating organisms since not one disinfectant is 100% effective against all organisms.

Reviewer's Assessment: *The disinfectants used at the Valneva Scotland Ltd. facility appear suitable and appropriately qualified. Additionally, overall facility cleaning was evaluated within the scope of the inspection conducted by ORA/OBPO on September 09, 2023.*

Critical Utilities

Water

Valneva purchases WFI for use in the manufacturing process and it complies with (b) (4) for Water for Injections (b) (4) requirements and with the (b) (4) for Sterile Water for Injection. Specifically, the WFI is used for (b) (4) step.

Reviewer's Assessment: *The WFI used in manufacturing is not produced on site. The qualification and monitoring of (b) (4) appears acceptable.*

HVAC

The HVAC system serving the (b) (4) clean rooms is fully segregated and is comprised of (b) (4) Air Handling Unit (AHU), which splits into (b) (4) zones. The (b) (4) total loss philosophy. There is (b) (4)

Each room served by the HVAC system has an air quality grade designed to comply with current EU GMP requirements. The qualification of the HVAC system covered the installation and operation qualification of the supply AHU and a service of the HEPA filter certification, supply flow rates, room pressure differentials and room particulates.

The differential pressures between the rooms of the (b) (4) cleanroom suite have been designed around a typical positive pressure cascade. In general, the differential pressure is at least (b) (4) between each subsequent level in the pressure cascade. Any changes to the pressure cascades are validated to ensure they meet the specifications for the product containment requirements. As per the pressure differential diagrams provided in the submission, the viral positive production areas

operate under containment as a negative pressure sink with positive pressure airlocks to protect the common corridors.

Reviewer's Assessment: HVAC design was reviewed and found acceptable. The HVAC requalification was reviewed in the inspection conducted by ORA/OBPO on September 09, 2023, and the inspection was classified as VAI.

Clean Compressed Air (CCA) and Process Gases

The (b) (4) Cleanroom Suite and the (b) (4) Cleanroom Suite each have an independent compressed air system. Compressed air is used for the actuation of pneumatically operated valves and for (b) (4) testing. In each system, the compressed air is supplied by (b) (4). The compressed air is provided at (b) (4) qualities: (b) (4). Compressed air is routinely tested to assure (b) (4) quality.

Reviewer's Assessment: A high-level description of the CCA and (b) (4) gases was provided and reviewed. The gas systems appear acceptable. Gases were reviewed within the scope of the inspection conducted by ORA/OBPO on September 09, 2023. The inspection was classified as VAI and no issues were noted.

Environmental Monitoring

Environmental monitoring is performed according to the set requirements for the defined room classifications. The activities for the Environmental Monitoring are documented in SOPs. These SOPs detail the sampling plans, sampling frequencies and associated procedures for environmental monitoring within the (b) (4) cleanroom suite.

Dynamic monitoring

Particle monitoring is carried out during the (b) (4) performed within a (b) (4) and during (b) (4) area (Grade (b) (4) air supply). (b) (4) are used for particle monitoring during production. Active air sampling in the (b) (4) is evaluated according to Grade (b) (4) limits, all other sampling locations are evaluated according to Grade (b) (4) limits.

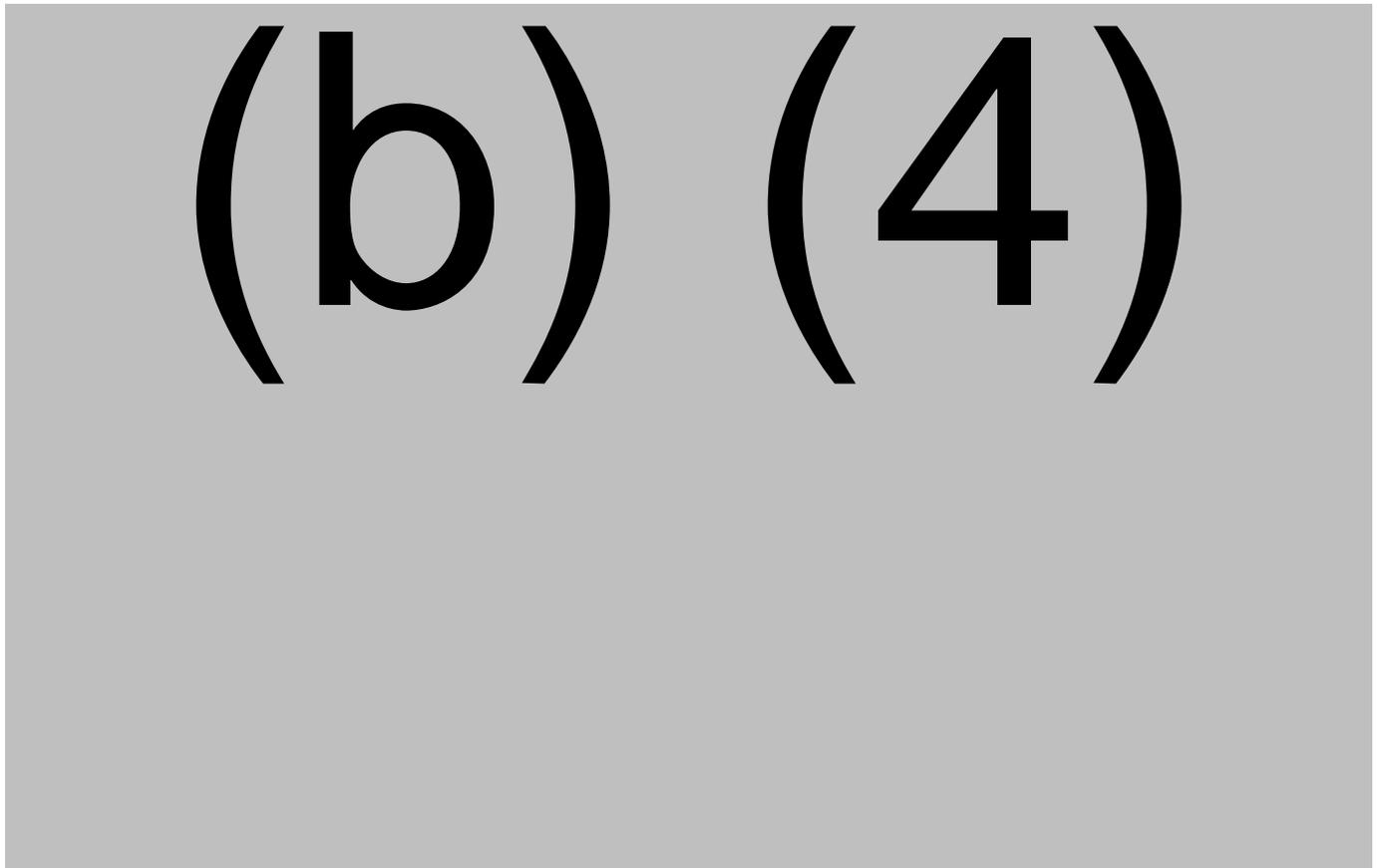
Environmental data is trended and reviewed to ensure a timely reaction to adverse trend.

Additional details regarding the environmental monitoring program at Valneva was provided in amendment STN 125777/0.61 (0060) in response to an information request. The information is summarized as follows. The EM program involves regular monitoring

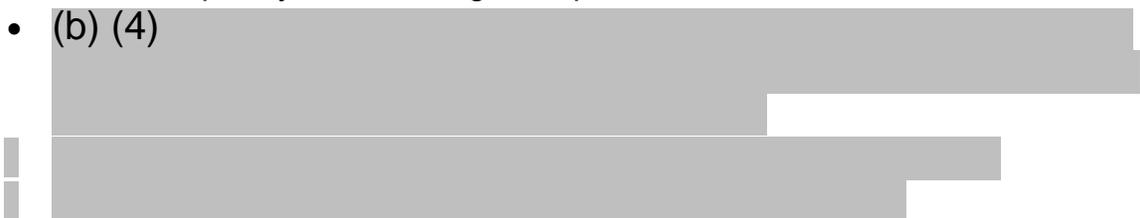
of non-viable and viable microorganisms in classified areas with monitoring performed to limits set in-house from the guidelines of standard (b) (4) FDA Guidance for Industry (2004) Sterile Products Produced by Aseptic Processing cGMP and from experience obtained from validation and periodic review of on-going EM data. A table for the in-operation action limits for classified areas were provided in detail. The non-viable particulate limits for particles (b) (4) provided were in alignment with the (b) (4) standards and detailed as follows:

- Grade (b) (4) action limit: (b) (4)
- Grade (b) (4) action limit: (b) (4)
- Grade (b) (4)

The microbial action limits were noted in the following table:



Details of the frequency of monitoring were provided as follows:

- (b) (4)
- 

Reviewer's Assessment: *The information provided for the EM program and routine monitoring appears acceptable. Additionally, the overall EM was evaluated in the scope of the inspection conducted by ORA/OBPO on September 09, 2023. The inspection was classified as VAI and no issues regarding EM were noted.*

Computer Systems

Information regarding the computer systems used at Valneva Scotland was provided in amendment STN 125777/0.61 (eCTD 0060) received July 6, 2023 in response to an information request since this information on the computer systems was not provided in the original BLA submission. This information is summarized as follows.

The validation of the computer systems at Valneva follows a (b) (4) model approach in which the computer system is evaluated and validated based on its complexity and intended use in the user requirement specification. The procedure is defined in SOPs MSOP-0042 "Validation of Computerized Systems", MSOP-0073 "Identification of Computerized Systems" and LIV-SOP-00625 "Validation of Computerized Systems".

Equipment with integrated firmware is assigned an identifier and is qualified and includes the validation requirements for a computerized system. Equipment that is connected to the Valneva network or uses individual user accounts to access the system, this is considered to be a computerized system.

Validation included IQ, OQ, PQ and is concluded before utilization of the system takes effect. Frequency and scope of periodic review are scheduled following completion of validation activities and are based on (b) (4)- criticality and defined specifications. There is (b) (4) computer system that is used to control a critical manufacturing process that included the use of the (b) (4) system. The firm confirmed completion of the qualification.

Reviewer's Assessment: *The information on the computer systems used at Valneva provided in amendment STN 125777/0.61 appears acceptable.*

Equipment

All GMP critical equipment were qualified, and systems validated. The measuring points of equipment are calibrated regularly in defined intervals. A table that includes a summary of the qualification of the equipment used for DS manufacturing including (b) (4)

(b) (4) and DS formulation were provided. The table included a brief description of the qualification testing performed for the equipment; details are noted as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

All process equipment is non-product contact and has been qualified for the intended use. All product-contact consumables are single use. The single use (b) (4) system utilizes single use disposables which come into contact with the product. Product is (b) (4)

(b) (4)

. No cleaning activities or product specific cleaning validation studies and/ or cleaning verification methods are applicable using single-use systems.

Part of the process design philosophy for the DS included the decision to opt for a single strategy for sterilization of consumables. Consequently, (b) (4) clean room suite, and (b) (4) is available for preparation of components. Many of the components and materials used in the manufacture of the DS have been supplied, following (b) (4) of sealed containers, by the manufacturer sterile ready for use. This is true of all the long-term product contact consumables, such as (b) (4)

(b) (4) for DS storage.

Reviewer's Assessment: *Equipment appears to be appropriately qualified for use. All product-contact equipment is single use thus no requirement for performing cleaning verification or validation.*

(b) (4)

(b) (4)

(b) (4)

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