

CBER CMC BLA Review Memorandum

BLA STN 125678/0

Product Name Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN)

Pete Amin CSO/CBER/OCBQ/DMPQ/MRB2

1. **BLA#:** STN 125678

2. **APPLICANT NAME AND LICENSE NUMBER**

Bavarian Nordic A/S

3. **PRODUCT NAME/PRODUCT TYPE**

Modified Vaccinia Ankara - Bavarian Nordic (MVA-BN)

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Pharmacological category: Viral Vaccine, Live
- b. Dosage form: Suspension for Injection
- c. Strength/Potency: 0.5 x 10e8 infectious units per 0.5 mL
- d. Route of administration: Subcutaneous
- e. Indication(s): Active immunization against smallpox in adults aged 18 years and older.

5. **MAJOR MILESTONES**

Filing Meeting: December 5, 2018

PDUFA Action Due Date: September 24, 2019

Date Received	Submission	Comments/ Status
10/25/2018	STN 125678/0	Review completed
2/21/2019	STN 125678/17 (response to IR #14, #29 and #30)	Review completed

6. **REFERENCED REGULATORY SUBMISSIONS (e.g., IND, BLA, 510K, MASTER FILE, etc.) - IND**

7. **REVIEWER SUMMARY AND RECOMMENDATION**

A. **EXECUTIVE SUMMARY**

BLA approval is recommended from the product quality perspective. T

B. **RECOMMENDATION**

I. **APPROVAL**

Drug Substance manufacturing facility:

Bavarian Nordic A/S
Hejreskovvej 10A,
3490 Kvistgaard
Denmark

Drug Product manufacturing facility:
(b) (4)

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Pete Amin/CSO/DMPQ	Concur	
Qiao Bobo, Branch Chief, OCBQ, DMPQ, MRB II	Concur	
John A. Eltermann, Jr., R.Ph., M.S. Director, DMPQ, OCBQ	Concur	

3.2.S DRUG SUBSTANCE¹

The active substance of the MVA-BN Smallpox vaccine (Live Modified Vaccinia Virus Ankara) is purified Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) live virus, a highly attenuated Orthopox virus, propagated in primary Chicken Embryo Fibroblast (CEF) cells.

3.2.S.2.1 Manufacturer(s)

Table 1: drug Substance Manufacturing Sites

Name and Address	FEI/DUNS Number	Responsibility
Bavarian Nordic A/S Hejreskovvej 10A 3490 Kvistgaard, Denmark	FEI: 3008318564 DUNS: 310209754	Drug substance manufacture. Storage of MSV and WSV Batch release of MSV, WSV and drug substance
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Manufacture of MSV and WSV

Table 2: Drug Substance Testing Sites

Name and Address	FEI/DUNS Number	Responsibility
Bavarian Nordic A/S Hejreskovvej 10A 3490 Kvistgaard, Denmark	FEI: 3008318564 DUNS: 310209754	DS, process intermediate and stability testing: (b) (4)
Bavarian Nordic (b) (4)	FEI: 3005565792 DUNS: 314328944	DS, process intermediate and stability testing: (b) (4)

(b) (4)

3.2.S.2.2 Description of Manufacturing Process

The Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) Drug Substance (DS) is produced under aseptic conditions starting with primary Chicken Embryo Fibroblast (CEF) cells prepared from embryos that are harvested from eggs of (b) (4) flocks of chicken. The CEF cells, (b) (4)

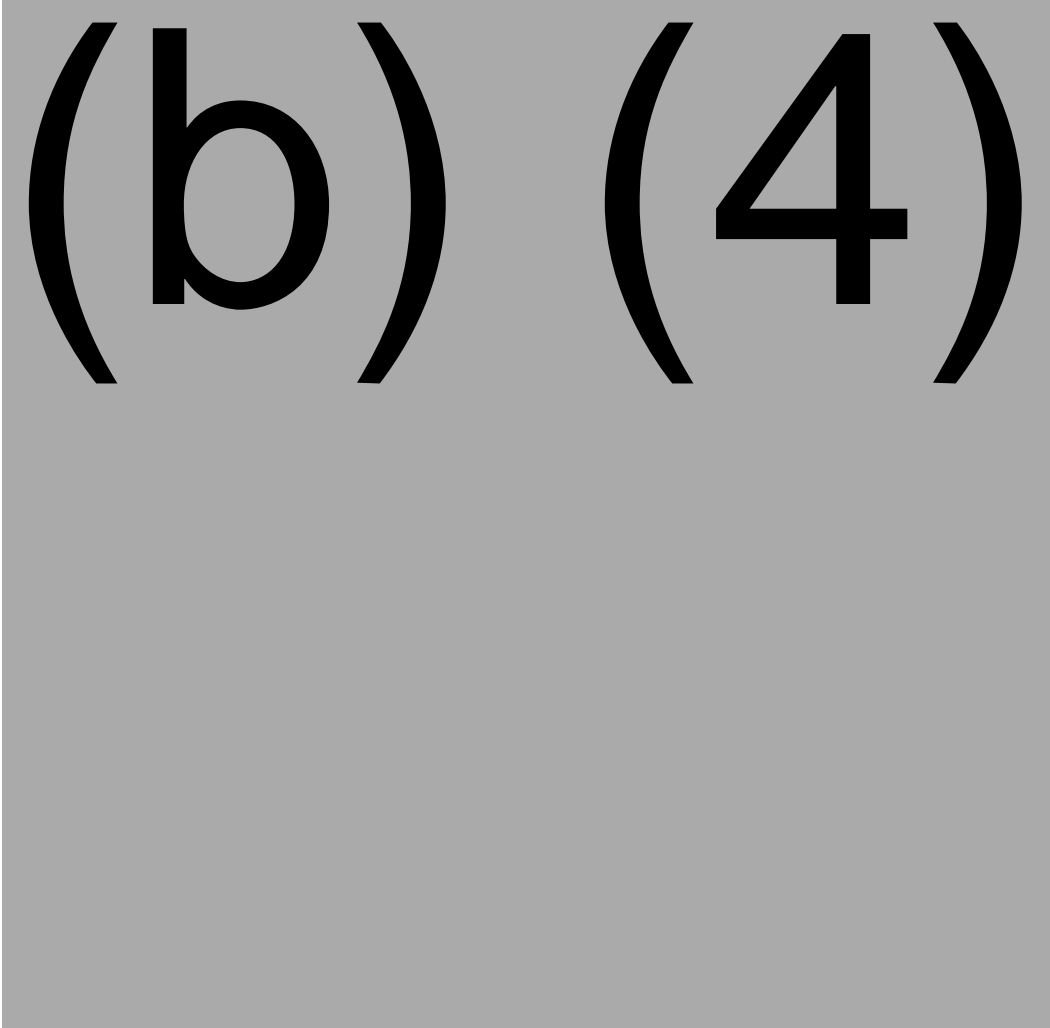
(b) (4), are infected with MVA-BN Working Seed Virus (WSV) (b) (4).

Following (b) (4), the (b) (4) virus harvest is purified and concentrated through several Tangential Flow Filtration (TFF) steps including enzymatic digestion by Benzonase for DNA size reduction.

The DS is stored at (b) (4) until formulation and filling.

□ **Manufacturing process steps**

The DS manufacturing process including information on scale using a (b) (4) CEF cell preparation process is provided in Figure 1 below. It illustrates the manufacturing process of DS including CEF cell preparation, virus growth, virus harvest and virus purification.



For each DS batch, the CEF cell preparation is performed in (b) (4)

(b) (4)

3.2.A.1 Facilities and Equipment

DRUG SUBSTANCE

Bavarian Nordic A/S (BN-K)- Drug Substance Facility

BN_K address:

Bavarian Nordic A/S (BN-K),

Hejreskovvej 10A

3490 Kvistgaard

Denmark

FEI#: 3008318564

BN_K facility: Inspection History

The BN-K facility is approved by the Danish Medicines Agency for manufacture of human medicinal products and human investigational medicinal products. BN-K has been inspected by the Danish Medicines Agency in 2012, 2014, 2015, 2016 and 2017, and by Health Canada in 2013. BN-K has been inspected by the FDA in 2009 and NIH in 2016.

Multi-product facility

The BN-K facility is a multi-product facility. The facility is used for production of commercial products (licensed products) and products under development (investigational medicinal products). The products manufactured in this facility are all viral vaccines. These consist of attenuated MVA-BN for smallpox indication as well as recombinant MVA-BN and recombinant Fowlpox vaccines for infectious diseases and oncology. All these products are considered BSL-1 materials. In addition, BN-K manufactures one recombinant Vaccinia vaccine that is considered a BSL-2 material. The table below lists the products manufactured in the same area as MVA-BN:

Building	Products Manufactured	Process Steps
Building (b) (4)	MVA-BN	Manufacture of Drug Substance
	Recombinant MVA-BN clinical trial materials	Manufacture of Drug Substance
Building (b) (4)	Recombinant vaccinia clinical trial material	Manufacture of Drug Substance
		Formulation, filling of Drug Product
		Manufacture of Master Seed Virus

	Recombinant MVA-BN clinical trial materials	Formulation, filling of Drug Product
	Recombinant FPV clinical trial materials	Manufacture of Master Seed Virus
		Manufacture of Drug Substance
		Formulation, filling of Drug Product

MVA-BN = Modified Vaccinia Ankara – Bavarian Nordic; FPV = Fowlpox virus.

Site plan:

The facility has (b) (4) buildings; buildings (b) (4) are for production of DS. Building (b) (4) is used for cell preparation [primary Chicken Embryo Fibroblasts (CEF)] and manufacturing by (b) (4). The manufacturing area of BN-K (Building (b) (4)) consists of Grade (b) (4) production rooms with Grade (b) (4) Biosafety Cabinets (BSC) or Laminar Air Flow (LAF) cabinets, Grade (b) (4) production rooms, Grade (b) (4) rooms for equipment washing and sterilization and a Grade (b) (4) autoclave area for handling of solid waste.

Review note: Building (b) (4) facility is not within the scope of this BLA 125678/0 review, BN-K will submit separate amendment in future to add the building (b) (4) facility.

Facility Layout Plan:

Material Flow:

Materials for the egg disinfection and processing are brought into the facility through the Grade (b) (4) area. Before transfer to the manufacturing area, each shipment of raw materials is examined to assure proper labeling and absence of damage. A unique material number is attached to each batch of raw material. Sampling is performed per established sampling plans, within a sampling hood designed to protect both product and operator. The resulting analytical report is reviewed, and the raw material is accepted or rejected by QA. Rejected materials are either returned to the supplier or destroyed. Only released raw materials are transferred to the production area in Building (b) (4) and used for manufacturing per manufacturing record requirements.

Review comment: BN_K provided material flow information found acceptable Material flow appears to be designed to prevent contamination and no review concern was raised.

Personnel flow:

Access to the Grade (b) (4) zone areas is limited to staff with documented training or to people accompanied by trained staff. There are designated areas for gowning appropriate for each zoning area. All entries into clean rooms are through air locks with interlocking doors. There are central lockers (rooms (b) (4)) located in the (b) (4) level for changing from outdoor to factory clothing. On entry into the manufacturing area personnel wear working garments and plant shoes or shoe covers. Personnel move with their clean clothes through corridors (b) (4) into the

Grade (b) (4) corridor (b) (4) and up the grade (b) (4) stairs (stairway (b) (4)). Personnel working in the CEF cell harvest and preparation area (rooms (b) (4)) enter through personnel airlock (b) (4) to sterile corridor (b) (4). Personnel working in the (b) (4) virus processes (rooms (b) (4)) enter through personnel airlocks (b) (4) to sterile corridor (b) (4) to sterile corridor (b) (4).

Waste:

Floor diagrams depicting the waste flow in Building (b) (4) (as part of the material flow diagram) is presented in Appendix 3. Cell preparation process waste is appropriately contained and leaves the cell preparation area via the material (b) (4) airlock (b) (4) and (b) (4) airlock (b) (4) to corridor (b) (4) and then corridor (b) (4). As this material has not been exposed to virus, it is not autoclaved but exits through corridors (b) (4) and out the waste airlock (b) (4) for disposal. Waste flow out of the cell area is procedurally controlled as materials are transferred in through the airlock in the morning and waste is removed in the evening.

Viral process waste is appropriately contained and exits the facility via (b) (4) waste material airlock (b) (4) to the (b) (4) to corridor (b) (4). After (b) (4), the waste moves through materials airlock (b) (4) to corridor (b) (4) and out the waste airlock (b) (4) for disposal.

There are individual (b) (4) for Building (b) (4), and a common (b) (4) waste. The waste system itself is disinfected as part of the campaign change over procedure. Solid waste from production is decontaminated in the (b) (4) to corridor (b) (4).

Review comment: BN provided a room classifications diagrams with an explanation of the manufacturing processes taking place, the room numbers and room classification (in operation/at rest). In addition, the material flow, personnel flow, and waste flow description were provided. I found the provided information acceptable and no cross contamination/mix up review concern was raised.

Equipment:

BN provides the list of equipment used for the primary chicken embryo fibroblast (CEF):

(b) (4)

Review comment: BN states that all equipment is qualified and cleaned before use. Equipment qualification and cleaning validation is covered in later part of this memo.

Following Equipment used at BN-K for DS manufacture using the (b) (4) (see provided in Table below). BN-k states that all equipment is qualified and cleaned before use.

Equipment	Room	Manufacturing Step	Usage Single/Multiple Product Contact/No Product Contact Equipment	Preparation, Cleaning, Sterilization, Storage
(b) (4)				
TFF	(b) (4)	Virus purification: (b) (4)	Multiple Use Product (virus) contact equipment	The TFF is cleaned by (b) (4) and sterilized by (b) (4). Cleaning is performed by automated (b) (4) using (b) (4).

Review comment: BN-K provided major equipment list which describes the location, process step each equipment used, and cleaning and sterilization method summary. Provided information found acceptable.

Major Equipment Qualifications

According to BN-K, all equipment is cleaned and qualified prior to use. The following equipment are the main equipment used in the DS manufacturing: (b) (4)

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

Facility Cleaning

(b) (4) is an (b) (4). They have a broad spectrum of antimicrobial activity. The (b) (4) disinfection agents are exchanged on a (b) (4) schedule to not create any risk of microorganism resistance towards one disinfection agent.

(b) (4) was chosen as the standard disinfection agent for the control of residual virus in areas exposed to open handling of virus and in case of spillage as it was shown to have a higher efficiency towards the viruses used in production. Booster cleaning after a production shut down consists of cleaning with (b) (4), then (b) (4) and finishing with a disinfection with (b) (4).

Disinfection Effectiveness Study:

The efficacy of the disinfectants used in the BN-K production facility was validated for the potential additional virus products. (b) (4) MVA-BN are both Vaccinia virus strains, in this study (b) (4) was chosen to represent other Vaccinia strains e.g. MVA-BN. (b) (4) were both tested in this validation study. All viruses manufactured in the facility are enveloped viruses and are readily inactivated by most chemical disinfection agents compared to non-enveloped viruses.

Surface Study ((b) (4) Evaluation)

(b) (4) were tested using (b) (4) for surface cleaning and disinfection based on the results of the suspension study. All (b) (4) viruses used in the suspension

study were also used in the (b) (4) test including (b) (4) (representing MVA-BN (b) (4)). The following (b) (4) representative surfaces were evaluated:

(b) (4)

(b) (4)

(b) (4)

Equipment Cleaning and Sterilization:

Most of BN's manufacturing operations utilizes single-use items for product contact surfaces, however, some product contact equipment is multi-use and are (b) (4). Some of the single-use items, such as the (b) (4) are also cleaned prior to use by (b) (4). Fixed equipment requires (b) (4) with each production batch (e.g. (b) (4), TFF systems (b) (4)).





Cleaning Validation and Cleaning Verification:

There are (b) (4) test plans for the cleaning validation studies: (b) (4). BN noted that for commercial products, cleaning validation was performed with validated programs on equipment used and with validated holding times. For Clinical Trial Material products, Cleaning Verification is performed (b) (4) each batch produced. The Cleaning Verifications performed include the same acceptance criteria as during validation, except for (b) (4) and holding times. Approved cleaning verification forms are used to register each Cleaning Verification performed.

Review comment: (b) (4) for TFF systems was covered during PLI. The cleaning validation including verification of acceptance criteria for visual inspection, (b) (4) for (b) (4) samples. All acceptance criteria were met. (b) (4) provided information found acceptable.

(b) (4)

(b) (4)



HVAC:

Building (b) (4) contains (b) (4) separate Air Handling Units (AHUs). AHUs units supporting the production area are qualified as they have an indirect impact on product quality. AHUs supporting the non-classified areas are commissioned but not qualified. The production area is equipped with (b) (4) HEPA filters.

AHU Qualification was initially performed in 2005 and consists of environmental monitoring during aseptic process simulations including monitoring of room conditions, particle level and microbial contamination. BN provided the IQ/OQ for the (b) (4) AHUs at BN-K.

Requalification of the HVAC systems includes reclassification (b) (4) of areas for particle counts, HVAC operation during shutdown periods, and HVAC operation during simulated production conditions. Requalification occurs according to internal procedures at defined intervals as described. The particle measurements are performed to re-qualify and ensure that the levels for particles (b) (4) in each room are under control and meets the requirements in accordance with the classification, without and with a defined number of persons in the rooms.

Review comment: HVAC system qualification was covered during PLI. HVAC qualification demonstrated all rooms met the room classification requirement under dynamic conditions.

EM:

Air is tested for occurrence of airborne viable and non-viable particles via (b) (4), where applicable. Surface testing for microorganisms is performed on walls, floors, and other surfaces with (b) (4) testing.

Particles are monitored (b) (4) by the Facility Management System (FMS) for Grade (b) (4) cabinets, Grade (b) (4) rooms and a single Grade (b) (4) room, while particle measurements are performed every (b) (4) in Grade (b) (4) airlocks and Grade (b) (4) rooms, and (b) (4) in Grade (b) (4) areas. An alarm is created in FMS every time an excursion of the alarm level is seen. Action limits for (b) (4) particulate sampling, including (b) (4) sampling, are established in internal procedures for Grade (b) (4) LAFs and BSCs; Grade (b) (4) production rooms, airlocks, and walkways; Grade (b) (4) Airlocks, walkways, and washing areas; and Grade (b) (4) walkways, and washing areas. The non-production related EM samples are executed at a fixed frequency before production activity and after cleaning, to establish a trend for the effectiveness of the cleaning procedures. For Grade (b) (4) the frequency is (b) (4) and for Grade (b) (4) the frequency is (b) (4). Production related EM samples are associated with the batch number and are executed with every batch. The sampling methods include (b) (4). In addition, (b) (4) on personnel with specified production related activities are sampled after each production related activity is completed. The acceptance criteria for EM for each production area is provided in Table below

(b) (4)

Qualification: The original EM Program Qualification (EMPQ, 82001012) was conducted in 2006 to ensure that the (b) (4) monitoring program provided meaningful information on the quality of the processing environment. Several issues were raised under the EMPQ and addressed. Trend analysis was performed in 2007 and 2008. An extended EMPQ was performed in 2009 (82001162) that consisted of an extended environmental qualification to ensure the routine environmental program provides the correct information on the quality of the environment in the production at BN-K with respect to the monitoring schedule and sampling positions. (b) (4) batches were produced during this time. This qualification focused on classified rooms in the grade (b) (4) and the airlocks (b) (4). Out of the (b) (4) samples taken in the (b) (4) rooms at BN-K, 99.33% were within the acceptance criteria. Two deviations were initiated one with five excursions and one with two excursions.

EMPQ was conducted in 2010 (82001110) due to an extension of the floor plan and another EMPQ was conducted in 2011 (70021276) with environmental and particle sampling made in rooms which are influenced by the commissioning of TFF (b) (4) located in room (b) (4). Sampling was performed (b) (4) times during a production day while the TFF in room (b) (4) was under operations and the samples were carried out for (b) (4) days. Rooms affected were (b) (4). No excursions

occurred during the qualification from the environmental monitoring or the particle monitoring.

Review comment: EM routine monitoring, and trend data was reviewed during PLI. EM program found adequate for the monitoring locations, test frequencies and established alert and action limits.

Computer Systems:

All utilities are controlled by local (b) (4)

(b) (4) Access to the systems (b) (4) is to log, display and archive process data, including alarms. The system also allows viewing of historical data and trend curves.

The HVAC units are controlled by the Building Management System (BMS), which provides monitoring, process control and recording of data for the ventilation units supporting the production building. Pressure control is performed by a stand-alone system. Operating room conditions (temperature, humidity, particle counts and pressure differences) are monitored by the Facility Monitoring System (FMS).

The performance of the ventilation system is continuously monitored through the FMS which monitors room pressure differentials, temperatures and humidity, as well as airborne particles in all production rooms.

Review comment: Dynamic computer system (material management system) validation was covered during PLI. BN states that all computer systems are qualified according to established validation protocols and including user specification, functionality, and system security.

3.2.S.6 Container Closure System

In 2016, Bavarian Nordic (BN) implemented a new storage temperature for drug substance (change from (b) (4) storage) which required a new container closure system to accommodate the (b) (4) storage temperature.

The company changed the storage container from (b) (4) to (b) (4) containers. Both storage containers are supplied by (b) (4)

(b) (4)

Review comment: BN provided the DS storage (b) (4) acceptance criteria for the (b) (4) . Provided information found acceptable.

Container Closure Integrity:

To confirm that the DS container closure system, (b) (4) container, with a filling range of (b) (4) stored at (b) (4) and packed in dedicated shipper boxes, meets the requirements defined for a combined transportation and CCI study and can retain a sterile barrier and adequate protection for the DS, the following test procedures were performed:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The combined transportation and CCI study of the (b) (4) containers demonstrated no failed results. No deviations were reported. During the routine stability program, CCI is confirmed by the (b) (4) test that is performed at start and end of shelf life (and end of the stability study). BN explained that the CCI study described above will be repeated at end of shelf life (presumably after (b) (4)).

Routine shipment:

Shipment of DS in (b) (4) containers is shipped in trucks from a Quality Assurance (QA) approved logistics provider. The (b) (4) containers is packed in (b) (4) shipper (insulated boxes with (b) (4)). All shipments include temperature monitoring from temperature loggers placed in the (b) (4) shipper. Normal transit time from the BN DS manufacturing site in Denmark to the DP filling site (b) (4) is around (b) (4).

Review comment: BN-k tested and qualified the new (b) (4) shipper, shipping validation with (b) (4) and CCI tests were performed. BN performed CCIT using the (b) (4) test and (b) (4) test. All acceptance criteria were met. Transport study demonstrated shipping container qualification and product protection during shipping. Provided information found acceptable. Additional clarification was requested (see IR questions regarding CCI and shipping validation).

DS- Batch Numbering, Pooling and Scale Definition

For the manufacture of one DS batch, at least (b) (4) eggs are used. BN validated production of full-size batches ((b) (4)), resulting in (b) (4) DS after concentration/purification by TFF) and reduced size batches ((b) (4)). Each (b) (4) holds (b) (4).

The DS batch numbering is assigned by an IT system called (b) (4). The batch numbering system is divided into a number series containing (b) (4) letters and (b) (4) digits. All batch numbers are unique and only used once. Batch number prefixes are assigned starting with the prefix, followed by (b) (4) digits (e.g. a (b) (4)).

Review comment: provided information found adequate.

3.2.S.2.3 Control of Materials

Raw materials are purchased as ready-to-use solutions from approved suppliers. Suppliers are approved by BN following an evaluation that provides adequate evidence that the supplier can consistently provide materials meeting the specification. The raw materials comply with (b) (4)

(b) (4) requirements whenever possible. Representative Certificates of Analysis (CoA) from the supplier and from BN as well as documentation of origins were provided for each raw material. BN explained that the first (b) (4) batches of each new raw material are subject to a full testing program. After the initial qualification, the full test program is only performed (b) (4) or on every (b) (4) batch of a raw material. Raw materials are categorized according to use and property.

Review comment: provided information found adequate. Detail review of this section was deferred to product reviewer of this BLA.

3.2.S.2.4 Controls of Critical Steps and Intermediates

BN provided the process controls for the MVA-BN DS manufacturing process at the BN-K site. Release tests, In-Process Control (IPC) tests, Process Monitoring tests (PMT), Process Parameters (PP), their acceptance criteria and justification were provided. The In-Process sampling points of the DS manufacturing process, the test method and acceptance criteria (AC) are as follows:

(b) (4)

(b) (4)









Review comment: (b) (4) step found acceptable. all other information provided in this section does not fall under the purview of DMPQ

Detailed summary of DS manufacturing:

BN provided detail summary of each process step in BLA and not repeated in this review memo. **Review comment:** BN provided process detail found acceptable.

(b) (4)



(b) (4)

(b) (4)

Review comment: hold time validation was part of stability/process development studies and reviewed by product office reviewer.

3.2.S.2.5 Process Validation and/or Evaluation







(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



INFORMATION REQUEST (IR):

Following section provides a summary of IR questions.

IR Review of Amendment 14:

BN-K provided response to FDA request for information in amendment #14 (IR was sent on February 13, 2018).

Question 1:

Please provide Qualification Summaries for equipment used in DS production such as:

(b) (4) etc.

Bavarian Response 1:

An overview of main production equipment including location in the building, information of use (single or multiple use) and product contact equipment, as well as a summary of

cleaning or sterilization, is provided. See equipment qualification section of this memo for detail.

Review comment: Response is adequate. (equipment qualification is covered in this memo, see equipment qualification section for detail).

Question 2:

Please provide the locations of the (b) (4) used in the (b) (4) Cycles for facility cleaning validation of the DS site (BN-K).

Bavarian Response 2:

(b) (4) are used as (b) (4) in the (b) (4) cycle for validation of facility cleaning. The temperature is controlled using the Facility Monitoring System (FMS) for room monitoring; no (b) (4) are used during the (b) (4) cycle. (b) (4) are used to monitor performance of the (b) (4) cycle. In total, there are (b) (4) CCP locations controlled with (b) (4) and (b) (4) in Building (b) (4). The layout of Building (b) (4) is shown in Figure 1 and a tabulated overview of all (b) (4) locations is provided in Table 1.

Review comment: Bavarian provided (b) (4) locations during the (b) (4) validation in the Table 1 (page 6, 7, and 8) and found that (b) (4) placed including worst case locations. Response is adequate.

Question 3:

Please clarify what the acceptance criteria is for the release testing of the DP for Bacterial endotoxins. In the Process Validation and Evaluation document in Section 3.2.P.3.5, the acceptance criteria for bacterial endotoxins is listed as (b) (4), however, the Specifications document in Section 3.2.P.5.1 lists the Bacterial endotoxin acceptance criteria as (b) (4) for DP release testing.

Bavarian Response 3:

During previous productions and PV runs, the acceptance criteria for the bacterial endotoxin specification was set as (b) (4). Upon review of the data and to align with the acceptance criteria for bacterial endotoxins of (b) (4) release, the acceptance criteria were tightened to (b) (4) for the initial BLA submission (125678/0). In response to Information request 2 (received on November 14, 2018), the acceptance criteria for bacterial endotoxins for drug product were further tightened from (b) (4) (SN0006 submitted 27- November-2018). The acceptance criteria were not retrospectively updated for the process validation runs presented in [Module 3.2.P.3.5] where the specifications valid at the time of the validation are listed. The current specifications valid for release of future commercial lots are outlined in [Module 3.2.P.5.1] and the justification of specifications including a historical overview is presented in [Module 3.2.P.5.6].

Review comment: Response is adequate. BN provided adequate justification and the acceptance criteria for bacterial endotoxins for drug product were further tightened from (b) (4).

Question 4:

The Media fill test for the DP filling is performed (b) (4) using (b) (4) run. Please provide a justification for using (b) (4) run.

Bavarian Response 4:

During initial validation in 2006, (b) (4) consecutive media fills were carried out successfully. Since then, product specific media fills are performed every (b) (4). This approach is consistent with the frequency and number of runs for media fill study defined in the FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing. The systematic approach of media fills at the DP contract manufacturer (b) (4) is based on the internal procedure SOP-000112 (Performance of Media Fills; available upon request on site). The procedure is based on FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing 2004 and on (b) (4).

Review comment: Response is adequate. (b) (4) verified that (b) (4) media fills were performed during initial qualification, followed by (b) (4) requalification. Media fill (DP) was covered in detail during PLI.

Question 5:

Please clarify if media studies were conducted incorporating the formulation step at the DP manufacturing facility.

Bavarian Response 5:

It can be confirmed that the aseptic process simulation (media fill) for MVA-BN DP filling at the contract manufacturer includes the relevant formulation steps including all (b) (4). The relevant documentation is available upon request on site at the contract manufacturer (b) (4).

Review comment: Response is acceptable. (b) (4) verified that media fill studies including the formulation steps.


Question 6:

Please clarify the media studies performed to qualify the aseptic processing in the DS manufacturing facility.

Bavarian Response 6:

BN0003039 describes the principles, responsibilities, procedure and frequency for the Aseptic Process Simulation (APS). APS is performed to verify the validity of the aseptic process and to requalify production personnel.

(b) (4)



Review comment: Response found acceptable.

DS- Additional IR (dated 07/15/2019, response date 07/31/2019):

Question 1:

Regarding Drug substance shipment study provided in your BLA the following was stated: "The shipment validation for the MVA-BN DS in the qualified (b) (4) shipper has not been performed yet since all DS batches manufactured after implementation of the (b) (4) containers are currently stored at BN-K for stockpiling and are commissioned for availability in a potential emergency-use situation. The shipment validation protocol, BN0003154 covers the shipment validation of (b) (4) of DS in (b) (4) containers in (b) (4) shipper at (b) (4)."

- a) Please provide anticipated timeline for conducting the proposed DS shipping validation as per Protocol BN0003154 including justification of number of shipment and worst-case conditions that will cover during this study.*
- b) Please describe your current DS shipping procedure that ensures adequate product protection during DS shipment.*

Bavarian Response 1:

An anticipated timeline for the validation of the DS shipping procedure per validation protocol BN0008665 "Shipping Process Validation, (b) (4) in (b) (4) Shippers - Shipment from BN-K to (b) (4)" cannot be provided yet. The next manufacturing campaign at (b) (4) has not been scheduled at this time point. The first shipment will represent the initial validation of the DS shipping procedure as described in SOP BN0003154 ("Standard Operating Procedure, Shipment Validation") and will at the same time mark the start of a (b) (4). During the (b) (4) study, all performed shipments will be monitored and evaluated. A validation report will summarize the (b) (4) study including an assessment of seasonal impact. The report will furthermore assess whether the (b) (4) period included enough shipments for final release of the shipping procedure.

Otherwise, the (b) (4) study will be extended to include additional shipments. Thereafter, the validation report will be updated to include the evaluation of the additional shipments. Further on, all routine shipments will be monitored and evaluated. However, no report will be written. Release of shipped material will be done as part of the batch release procedure.

In general, the shipping validation is performed to ensure that the shipping conditions. The shipment validation during the (b) (4) study will assess routine shipments performed to transport the drug substance from the DS manufacturing facility to the Drug Product manufacturing facility. Besides including (b) (4) conditions, the shipments will not include additional challenges.

All DS stored in the same (b) (4) as MVA-BN DS is shipped using the (b) (4) shipper to ensure adequate product protection during DS shipment. The shipments performed so far were all for clinical trials and partners where BN was only responsible for the packaging. The qualified (b) (4) shipper will be used for shipment of MVA-BN DS. (b) (4) container

are packed in (b) (4) shipper as instructed by the (b) (4) shipper supplier and specified in internal procedures


Temperature loggers will be placed in and on the (b) (4) shipper measuring the temperature during the shipment. (b) (4) calibrated temperature loggers as specified in the sensor location diagram presented in Figure 2 are placed within the shipper above and below the (b) (4) container (location 1 and 2) and the sensor numbers are recorded. Additional (b) (4) shippers in the same setup will be added to the shipment if additional DS will be shipped during the same transport. Again, (b) (4) temperature loggers are placed in each (b) (4) shipper.

Upon arrival, the DS in the (b) (4) is removed from the shipper. The study end time is recorded. Temperature loggers are sent back to BN for data read out and final shipment release. Data will be retrieved and evaluated to verify that the temperature was kept to (b) (4).

Review comment: Response found acceptable.

Question 2:

(b) (4)



(b) (4)

3.2.P DRUG PRODUCT

MVA-BN Drug Product (DP) is manufactured at the contract manufacturing organization (b) (4). It includes the manufacturing of the formulation buffer and bulk DP.

(b) (4) Facility

The manufacturing facility of (b) (4)

:

(b) (4)

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

MVA-BN is provided as a single-use, sterile, preservative-free, liquid-frozen suspension for subcutaneous injection containing a dose of 0.5 mL with at least 0.5×10^8 Infectious Units of MVA-BN. The virus is grown in Chicken Embryo Fibroblast (CEF) cells, harvested and purified.

The DP is supplied as a frozen suspension in a 2 mL vial containing 0.5 mL extractable volume of the vaccine. A target fill volume of (b) (4) mL was established to ensure an extractable volume of ≥ 0.5 mL. The DP does not contain any adjuvants or preservatives but may contain trace amounts of residual host cell DNA and protein, benzonase and the antibiotic gentamicin.

The vial is made of (b) (4) borosilicate glass which is closed with a sterile bromobutyl rubber stopper, crimped with an aluminum cap and covered with a polypropylene closure.

Review comment: provided drug product description found acceptable.

3.2.P.3.3 Description of Manufacturing Process

Manufacture of the DP consists of (b) (4) DS with the formulation buffer to bulk DP and filling into single dose vials, followed by inspection, labeling and packaging of the vials. Afterwards the MVA-BN vials are visually inspected. A production batch size is (b) (4) vials.

A detailed description of the manufacturing process is included below:

(b) (4)

Filling

DP is filled on Line (b) (4) in building (b) (4)

(b) (4)

The cleaned, dried and sterilized vials are conveyed completely automatically under the filling needles, where the vials are filled (b) (4) at a time. The filling volume is (b) (4) (b) (4). Once filled, the vials are fed to the stoppering unit, closed with sterile rubber stoppers and then fed to the crimping machine, where they are sealed. The filling, closing and crimping speed is approximately (b) (4) vials/min.

Visual inspection, Labeling and Packaging of Vials

The closed vials are transferred (b) (4) to a packaging line located in building (b) (4) in a temperature-controlled van (at a transport temperature between 2°C and (b) (4)). The vials are visually inspected semi- automatically prior to labeling. Visual inspection is performed at (b) (4) (b) (4). Labeling is performed automatically at approximately (b) (4) (b) (4).

(b) (4) vials are placed in a plastic blister tray; (b) (4) trays are contained in one folding box. A shipment box contains (b) (4) folding boxes. Labeling and packaging is done at (b) (4) (b) (4). The packaged product is transported from the packaging area to the cold storage (2 - 8°C) (b) (4) and placed on pallets.

Freezing and Storage

The entire batch is frozen under controlled conditions at (b) (4) in a (b) (4) (b) (4) for at least (b) (4). Finally, the pallet is transported to the storage freezer (-20°C) and stored until shipment. Long term storage of the final DP is at -20°C ± 5°C (max. 36 months) (b) (4) (b) (4).

(b) (4) facility

The main MVA-BN manufacturing activities are conducted in Building (b) (4) (b) (4).

Building (b) (4):

(b) (4) provided the material and personnel flow diagrams and the general layout of building (b) (4). Filled DP vials are 100% semi-automatically visually inspected in building (b) (4), room (b) (4), for any defects of the vials, correct closure and appearance of the final DP.

Building (b) (4):

The (b) (4) facility is designed as a multi-product manufacturing facility. Products are filled on a campaign basis, with only one product manufactured at one time within a filling line area, (for MVA-BN the filling area of line (b) (4) consists of rooms (b) (4) (b) (4)). In the corridors, any material moved is boxed in trays and appropriately labeled. For manufacture of the MVA-BN DP, dedicated product-contact equipment is used.

Manufacture of the MVA-BN DP is carried out in the Pharmaceutical Manufacture area where manufacture, filling and visual inspection of other drugs take place.

The following product classes are handled in building (b) (4) (b) (4):

(b) (4)

Specifically, on filling line (b) (4) where MVA-BN is filled, (b) (4)

are processed.

Environmental Control in (b) (4)

(b) (4) stated that EM is established in all classified rooms in building (b) (4). EM monitoring is divided in the following: Routine monitoring and batch-related monitoring. The EM program includes Active and Passive air sampling to include viable and non-viable testing.

Review comment: (b) (4) didn't include detailed EM program information; additional IR was requested (see IR regarding EM program)

DP Material and Personnel Flow in (b) (4)

Material Flow

(b) (4) provided floor diagrams depicting material flow in building (b) (4). The formulation buffer is prepared in room (b) (4). Weighing of the buffer occurs in room (b) (4). After preparation, the formulation buffer is stored in a cold room in building (b) (4) and is transported via airlocks to room (b) (4) for compounding and filling.

DP is formulated in room (b) (4)

DS (b) (4) are transferred, (b) (4)

and the appropriate amount of formulation buffer is added. Vials and material supply of DS is transported into room (b) (4). The sterile stoppers and caps are transported to filling room (b) (4).

DP is filled on filling line (b) (4). The (b) (4) filling line was constructed in 2004 and commissioned in 2005. The filling line is a compact-unit with a washing machine and a sterilization tunnel in room (b) (4), a filling and closing machine in room (b) (4), and a crimping machine likewise in room (b) (4). Product exits through room (b) (4) via conveyor belt.

Review comment: Material flow information found adequate.

Personnel Flow

(b) (4) provided floor diagrams depicting personnel flow in building (b) (4). All entries into clean rooms are through air locks. Movement of personnel through the air locks, as well as gowning requirements for each area, are governed by SOPs.

Review Comment: Review of the personnel flow appears adequate.

Waste Flow

(b) (4) provided floor diagrams depicting waste flow in building (b) (4). Product residuals are collected in appropriately labeled and locked waste-containers and are transported to disposal. Contaminated equipment and clothes are collected in closed (b) (4) containers, which are then delivered via airlock to another department for inactivation.

Review Comment: Review of the waste flow appears adequate.

Equipment

Product contact equipment in the manufacturing area at (b) (4) are made of (b) (4), however when (b) (4) is not possible, (b) (4) liners are used. In addition, dedicated (b) (4) are used for the transport of the product during manufacture. All equipment carries a qualification certificate together with product-related cleaning instructions. A list of the equipment and auxiliary materials used at (b) (4) for the preparation of the formulation buffer, bulk DP and the final DP manufacturing process is provided in Table 60 below.



Equipment/Model used for DP Production	Supplier (e.g.)
--	-----------------

(b) (4)	(b) (4)
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4) vessel, formulation	
Autoclave (b) (4)	
Line (b) (4) (vial filling line)	
Washing machine (b) (4)	
Sterilization tunnel (b) (4)	
Filling and stoppering unit (b) (4)	
Capping Station (b) (4)	
(b) (4) station	
Gross weight balance	

All product contact equipment used for formulation and filling is dedicated and shown in the table as shaded.

Review comment: Cleaning and sterilization validation was completed for all product equipment and validation reports were reviewed during the PLI. All equipment were qualified.

Equipment Qualification

Qualification and calibration of equipment follow written procedures which also defines frequency of cleaning and maintenance. A re-qualification is also performed depending on the equipment. Detailed schedules are documented in a validation master plan. The table below provides a schedule of frequency and action to be taken on the equipment listed.

Table 61, Frequency and measures of re-qualification

Equipment	Action	Requalification interval
(b) (4) vessel, buffer prep (b) (4)	Recalibration Periodic Review	(b) (4)
(b) (4)	Recalibration Periodic Review	
(b) (4)	Recalibration Periodic Review	
(b) (4) vessel, formulation	Recalibration Periodic Review	
Autoclave (b) (4)	Recalibration Revalidation Periodic Review	
Line (b) (4) (vial filling line)	Media Fill Periodic Review (whole system) Recalibration (b) (4)-Test	
Washing machine (b) (4)	Recalibration	

Equipment	Action	Requalification interval
Sterilization tunnel (b) (4)	Recalibration (b) (4)-Test (b) (4) test	(b) (4)
Filling and stoppering unit (b) (4)	Revalidation of (b) (4) Revalidation of (b) (4)	
Capping Station (b) (4)	N/A	N/A

Qualification of the Multi-Use equipment such as Filling Line (b) (4) Vessels, and the autoclave are discussed below.

Qualification of Filling Line (b) (4):

Filling Line (b) (4) includes the washing machine, dry heat tunnel, filling line and stoppering machine. Initial qualification of Filling Line (b) (4) was performed in April 2005 (which included IQ/OQ). The items included in the IQ/OQ included: FAT, check for completeness and intactness, technical documents, check of IQ distributor, check for correct software, URD, Logbook, maintenance plan, first cleaning, SOP, training, calibration, functional and performance test, (b) (4) test washing machine, temperature distribution in the tunnel, data backup and (b) (4)-Test. Several re-qualifications have occurred over the life-cycle and a listing of frequency is provided in Table 61 above.

Review comment: provided filling line (b) (4) qualification information found acceptable.

Qualification of (b) (4) Vessel:

(b) (4) provided a list of items covered in the OQ of the (b) (4) Vessel and stated that all parameters were met. Those parameters included: (b) (4)

Review comment: (b) (4) Vessel qualification information found acceptable.

Qualification of the Autoclave (b) (4):

Initial qualification was finished in August 2005. Validation programs is established, and revalidation of sterilization programs occurs every year. The items covered in the IQ/OQ/PQ for the qualification of the autoclave included: FAT, Check for completeness and intactness, technical documents, Check of correct software, URD, Logbook, Maintenance plan, SOP, Training, Calibration, Functional and performance test of several programs, including temperature distribution in the (b) (4) (OQ of distributor), and Initial Validation of programs. (b) (4) reported that all parameters were met.

Review comment: Autoclave qualification information found acceptable.

Cleaning and Sterilization of Key Equipment:

Cleaning validation for the multi-use equipment include the following:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Cleaning of equipment before and after filling:

The (b) (4), buffer prep and the (b) (4) formulation vessel are (b) (4) sterilized before use. The cleaning is validated (b) (4) while sterilization is validated (b) (4). After filling, the (b) (4) vessel is (b) (4) with (b) (4) cleaning solution and the formulation vessel is cleaned with a (b) (4) cleaning solution for inactivation and both are (b) (4) sterilized. (b) (4) performs (b) (4) revalidation of the cleaning and (b) (4) validation of sterilization.

Autoclave (b) (4) is cleaned with (b) (4) filling (no product contact). The washing machine ((b) (4)) uses (b) (4) to clean vials (b) (4) filling and the cleaning validation is done by (b) (4). After filling, the washer is cleaned as part of the line clearance. The sterilization tunnel ((b) (4)) is cleaned using (b) (4) sterilization before filling and is validated by an (b) (4) test. After filling, the sterilization tunnel cleaning is part of the line clearance. The Filling and stoppering unit ((b) (4)) is (b) (4) sterilized before and after filling. Cleaning is validated (b) (4), and sterilization is validated (b) (4).

Review comment: cleaning validation was covered during PLI. (b) (4) provided cleaning validation information was found acceptable.

Water systems

The water supply in building (b) (4) consist of (b) (4)

(b) (4)

(b) (4)

Review comment: Water system provided information found acceptable, however additional IR was requested for the (b) (4) system (see information request (IR) request)

HVAC

(b) (4) provided a diagram of the pressure differentials in building (b) (4). Table 62 below provides a summary of the pressure cascades in the different classified rooms.

(b) (4)

(b) (4) provided a diagram of the AHUs used in the facility. Separate air-conditioning systems with (b) (4) pre-filters are installed for ventilation of the sterile area. Air is passed through terminal (b) (4) HEPA filters. The air exchange rates are provided in Table 63 below.

(b) (4)

Review comment: HVAC provided system information found acceptable, however additional IR was requested for the HVAC system

Control of Cross Contamination

Product change over

Line clearance is performed (b) (4) filling. All parts of the filling line are checked for residual primary packaging materials and any found are removed. The filling line is (b) (4) as discussed earlier. In rooms (b) (4) all material is removed, and the rooms are cleaned and disinfected. Subsequently, (b) (4) is performed at line (b) (4).

Product segregation

As mentioned previously, products are manufactured on a campaign basis at the (b) (4) facility, with only one product manufactured at one time in the filling area. (b) (4) does however, perform parallel filling in separated filling line areas. They explained that all

filling lines have their dedicated and separated staging areas. Packaging and inspection are performed in divided rooms. The sealed vials are packed into boxes in room (b) (4) in sub-batches. Boxes are then sealed, and an interim label is affixed to the boxes prior to leaving the designated clean room area. The sub-batches are subsequently transported to room building (b) (4) room (b) (4) for visual inspection.

Production area sanitization

The production area in building (b) (4) is supplied from a service floor located above the manufacturing rooms.

Water system in building (b) (4): After each (b) (4), the AP-producer is sanitized with (b) (4) for over (b) (4).

(b) (4)

The manufacturing area is decontaminated by (b) (4) after each (b) (4). Details on the cleaning reagent, duration and concentration are laid down in the internal provisions.

Review comment: Over all provided cross contamination control approach found acceptable, IR was requested for the (b) (4) effectiveness study.

3.2.P.2 Pharmaceutical Development

Deferred to product reviewer (except CCI study)

3.2.P.2.1 Components of the Drug Product

The information provided in this section does not fall under the purview of DMPQ (Deferred to product reviewer except container closure system)

3.2.P.2.1.1 Drug Substance

The Drug Substance (DS) consists of purified MVA-BN virus in a Trometamol-NaCl buffer (10 mM Tris containing 140 mM NaCl, pH 7.7). (deferred to product reviewer of this file)

3.2.P.2.1.2 Excipients

BN reported that no excipients of human or animal origin or novel excipients were used in the manufacture of the DP. (deferred to product reviewer of this file)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

(deferred to product reviewer of this file)

3.2.P.2.2.3 Physicochemical and Biological Properties

Deferred to product reviewer of this file.

3.2.P.2.3 Manufacturing Process Development

An industrial scale process was validated at (b) (4) and consisted of (b) (4) DP consistency lots ((b) (4)). Lot (b) (4) produced in November 2005 ((b) (4) doses) as one of the validations lots. Using the commercial manufacturing process at BN-K and (b) (4) DP lots ((b) (4)) were formulated and filled in May 2012 from (b) (4) DS lots.

Review comment: The information provided in this section does not fall under the purview of DMPQ

3.2.P.2.4 Container Closure System

Materials of construct for the container closure system for the DP are presented in Table 26 below:

Table 26, Components of the Container Closure System

Component	Description	Identity of material	Supplier	Compliance status
Vial	2 mL	(b) (4) clear borosilicate glass	(b) (4)	Complies with (b) (4) for (b) (4) glass
			(b) (4)	Complies with (b) (4) for (b) (4) glass
Stopper	13 mm grey rubber stopper	Bromobutyl compound with silicate filler (is made without natural rubber latex, chemicals associated with nitrosamines, di(2-ethylhexyl) phthalate or other phthalates or 2-mercaptobenzothiazole or any of its derivatives) (b) (4)	(b) (4)	Complies with (b) (4) requirements
Cap	13 mm silver/ yellow cap	Aluminum cap with polypropylene closure (flip tear up),	(b) (4)	Complies with (b) (4) Requirements

(b) (4) verified critical dimension as part of acceptance criteria and verification of certificate of analysis results.

(b) (4) conducted the (b) (4) of vials to demonstrate the effect of cold temperature. (b) (4)

3.2.P.2.5 Microbiological Attributes

The MVA-BN drug product is supplied as a sterile product and the formulation does not contain any preservative. A test for sterility is performed on the (b) (4) on the drug product, as part of the release testing. A test for bacterial endotoxins is performed (b) (4) on the drug product, as part of their respective release testing. The integrity of the container closure system was verified carrying out (b) (4) tests and a (b) (4) test by (b) (4). The integrity of the container closure system is also determined during stability testing. A container closure integrity test is performed (b) (4) and at the end of the stability study, and a sterility test is performed at the end of the stability study.

Review comment: Method validation for sterility and endotoxin method was reviewed by DBSQC reviewer for this file. I verified DP conformance lots sterility and endotoxin results. All results met acceptance criteria.

3.2.P.2.6 Compatibility

The vaccine is supplied as a suspension for injection. No reconstitution diluents are required for the vaccine. The compatibility of the DP with the container closure system was confirmed during leachable/ extractables studies and stability studies.

Review comment: Extractable/leachable study review was deferred to the Product Office.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Manufacture including labeling and packaging of the MVA-BN DP is performed at:

(b) (4)

(b) (4)

Drug product storage and release is conducted by:

Bavarian Nordic A/S (BN-K)
Hejreskovvej 10A
3490 Kvistgaard
Denmark

Testing of the DP may be performed at the following sites:

(b) (4)

Bavarian Nordic A/S
Hejreskovvej 10A
3490 Kvistgaard
Denmark

Bavarian Nordic (b) (4) (BN-^{(b) (4)})
(b) (4)

(b) (4)

3.2.P.3.2 Batch Formula

Review comment: Deferred to product office.

3.2.P.3.4 Controls of Critical Steps and Intermediates

(b) (4) describes each process step, the monitored parameter, its acceptance criteria along with justification.

(b) (4)

(b) (4)

Review comment: During process validation, above filling process parameters were monitored and met acceptance criteria. Provided information found acceptable.

Shipping DP

(b) (4) provided the shipping criteria for time and temperature as follow:

Transport time	(b) (4)	Transport is usually conducted in (b) (4).
Transport temperature	(b) (4)	Normal operating range for the transport temperature is (b) (4) the criteria of up to (b) (4) is for acceptance of increase in temperature reading when opening the doors. Temperature is not likely to exceed these limits.

Review comment: The shipping condition was validated. See additional information in the section “shipping validation.”

Visual Inspection

(b) (4) describes the critical parameters for their semi-automatic visual inspection process as follow:

(b) (4)

Review comment: (b) (4) validated their visual inspection process. Additional IR was sent regarding visual inspection process.

Labeling and Packaging:

Following table describes the critical parameters for the labeling and packaging process:

Print of variable data on vial labels	Conforms to batch record	The printing of the variable data is performed using an automated, validated system. 100% camera control is performed on the print. The variable data is confirmed in the batch record every (b) (4) and following production breaks.
Placement of blisters in secondary boxes	(b) (4)	The main part of the batch blisters is transferred automatically from the blistering robot to the cartoning machine. Control of the manually blistered vials is included in the master batch record and manufacturing instruction. All folding boxes packed with manually blistered vials are controlled for correct position of vials prior to packaging into shipper boxes.
Print of variable data on secondary boxes	Conforms to batch record	The variable data is confirmed in the batch record every (b) (4) and following production breaks.

Review comment: (b) (4) provided information regarding labeling and packaging critical parameters and found acceptable. Additional IR was requested for labeling process.

(b) (4) freezing

Following critical parameters were established for the (b) (4) freezing process.

(b) (4)

Review comment: Additional IR was requested for the (b) (4) freezing process.

DS Storage

(b) (4) provided following DS storage parameters:

(b) (4)

Review comment: Additional IR was sent for DS storage process.

DP Releases test:

(b) (4) provided information on the release tests for process intermediates and IPCs.

Formulation buffer tested for (b) (4)

(b) (4) drug product tested for pH, (b) (4), and sterility.

Visual inspection including the AQL test. The AQL action limits for Critical defects (b) (4)%, Major defects (b) (4)%, Minor defects (b) (4)%, and Product-specific particulate.

Final drug product is tested for appearance, pH, extractable volume, identity, sterility, virus titer, total protein, and endotoxin.

(b) (4)

(b) (4)

Review comment: (b) (4) provided information for the formulation buffer release test, (b) (4). The provided information found acceptable. Release tests method validation and justification of acceptance criteria were deferred to product reviewer.

3.2.P.3.5 Process Validation and/or Evaluation

An overview of the MVA-BN DP process validation studies and the year performed is described below:

Table 29, Overview MVA-BN DP Process Validation Studies

Year	Process Validation Study	Description
2005	Validation of the DP manufacturing process	Initial process validation. Performed on Filling Line (b) (4) at (b) (4), validated DS batches were used.
2007	Validation of the DP manufacturing process	The MVA-BN DS manufacturing process was transferred from (b) (4) to BN-K. The DP process remained unchanged but was transferred to a different filling line (Line (b) (4)) at (b) (4). The commercial-scale DP process was revalidated at (b) (4). The validation consisted of the production and filling of (b) (4) DP lots at (b) (4) on Line (b) (4) using DS from the new source (BN-K).
2008	Validation of the DP manufacturing process	Following technical optimizations, the commercial manufacturing process was revalidated.
2014	Validation of the DP manufacturing process	The manufacturing process was adapted with continuous process improvements without implementing major changes. The process was revalidated by manufacture of (b) (4) DP lots at set points.

The process validation comprised (b) (4) consecutive DP lots ((b) (4)) manufactured at (b) (4). The validation took place in the period of July 2014. The validation was performed under a Process Validation Protocol (Validation Protocol, FDP Process Revalidation, doc. no. 820001314) and documented in a Process Validation Report (Validation Report, FDP Process Revalidation, doc. no. 820001315).

The validation was performed at set points according to predefined acceptance criteria.

(b) (4)

Review comment: As shown in table above, all (b) (4) conformance lots met process parameters including (b) (4)

Release testing of (b) (4) the final DP also complied with the acceptance criteria including sterility, endotoxin, appearance, total protein, extractable volume, virus titer, and packaging control.

(b) (4) also performed a stability study to validate the formulation buffer holding time. (b) (4) batches of formulation buffer were kept at (b) (4) in (b) (4) and tested at regular intervals ((b) (4)) for (b) (4). The results support a holding time of (b) (4) for the formulation buffer kept at (b) (4).

Media fills:

Media fills are performed routinely to qualify the aseptic filling process. (b) (4) uses dedicated product contact equipment for their filling on Line (b) (4). Aseptic filling process validation of filling line (b) (4) is performed (b) (4) and consists of (b) (4) successful media fill run. Each media fill run consists of a (b) (4)

Operator interventions increase the exposure time of open vials within the filling line. Thus, 'worst case' conditions of filling are applied during media fills and media fills can be regarded representative for the routine filling process. The acceptance criterion is no positive contamination. The latest media fill was performed in 2017 with passing results. (b) (4) reported no turbidity was detected in any of the vials during media fill.

Media Fill 2017

Batch	Number of filled Vials	Filling Volume	Filling Time	Vials (b) (4)	Acceptance Criteria fulfilled
(b) (4)					Yes

Reviewer Comment: Media fill provided information found acceptable, however an information request Q4, dated February 13, 2019, clarification was requested for using only (b) (4) media run for the media fill test.

BN-K explained that during initial validation in 2006, (b) (4) media fills were carried out successfully. Since then, product specific media fills are performed every (b) (4). This approach is consistent with the frequency and number of runs for media fills defined in Section IX. A. 2. of the FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing. The systematic approach of media fills at the DP contract manufacturer (b) (4) is based on the internal procedure SOP-000112 (Performance of Media Fills; available upon request on site). The procedure is based on FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing 2004 and on (b) (4).

Reviewer Comment: In an information request Q5, dated February 13, 2019, clarification was requested. if media studies were conducted incorporating the formulation step at the DP manufacturing facility.

BN-K confirmed that the aseptic process simulation (media fill) for MVA-BN DP filling at the contract manufacturer includes the relevant formulation steps including (b) (4). The relevant documentation is available upon request on site at the contract manufacturer (b) (4).

Reviewer Comment: Response is adequate.

Container closure – cleaning and sterilization

The vials, stoppers and caps are delivered clean washed to (b) (4). There they are sterilized/ autoclaved. (b) (4) stated that the validated sterilization cycle meets a sterility assurance level (SAL) of (b) (4).

Review comment: (b) (4) states that sterilization cycle meets a sterility assurance of (b) (4) and found acceptable. Additional clarification was requested (IR) for the container closure washing and sterilization validation.

Autoclave cycle validation

A prospective validation for the sterilization of process equipment and (b) (4) in the autoclave (from (b) (4)) was carried out in 2009. The revalidation was scheduled (b) (4) times per year until 2017, including (b) (4) runs per revalidation. Since 2018, the revalidation will be performed annually, including (b) (4) revalidation run. The latest revalidation from May 2018 is summarized below:

(b) (4) describe the sterilization validation procedure. Data loggers and (b) (4) were placed at the critical locations ((b) (4) placements determined during qualifications). The temperature was recorded at (b) (4) interval. (b) (4) were homogeneous at all

measuring points during the sterilization phase. The acceptance criteria of (b) (4) were fulfilled at each measuring point. All temperature sensors clearly recorded temperatures (b) (4) before starting of the sterilization phase; this means that the (b) (4) to be sterilized is independent from its position in the autoclave. There was no significant hot or cold spot in the device. The required F₀-value (b) (4) could be recorded at each measuring point. During the sterilization phase, the recorded data of all sensors (temperature/pressure) as well as the recorded data of the autoclave (temperature/pressure) showed the existence of saturated steam conditions (b) (4). The microbiological analysis of the (b) (4) clearly showed the efficacy of the sterilization process. The autoclave load pattern is presented and found acceptable.

Review comment: Autoclave cycle validation provided information including the (b) (4) study and study results found acceptable.

Formulations Vessels- (b) (4) Validation

For the DP manufacturing process of MVA-BN (b) (4) formulation buffer tank, (b) (4) for media fill and (b) (4) formulation tank, equipped with a (b) (4) unit. (b) (4) performed the initial qualification of (b) (4) tanks was performed in 2009. The performance of all tanks during the qualification runs was found satisfactory. The tanks are requalified every (b) (4) years according to internal procedures (periodic review).

(b) (4) validated their (b) (4) of the (b) (4) vessels using a (b) (4) provided the diagram in BLA showing the location of the sampling points. (b) (4) and (b) (4) sample identified as worst case and tested during validation. The (b) (4) samples were tested for (b) (4) and (b) (4) samples were tested for (b) (4). All samples met acceptance criteria.

(b) (4) also validated their (b) (4) procedure of the (b) (4) vessels by using the (b) (4)

(b) (4)

(b) (4) reported that all relevant parts of the vessels were (b) (4) and none of the (b) (4)

Review comment: (b) (4) provided information found acceptable.

Filling line (b) (4) - cleaning/sterilization

Cleaning validation of filling line (b) (4) was first performed in 2005. Revalidations are performed (b) (4).

Cleaning validation covered the following substance groups:

- Readily soluble substances – (b) (4) cleaning agents
- Readily soluble substances – (b) (4) cleaning agents
- Readily soluble substances – (b) (4) cleaning agents, (b) (4) subgroup
- Readily soluble substances – (b) (4) cleaning agents

Cleaning and sterilization took place by means of a (b) (4) program executed by the automatic controller of the filling line. Following cleaning of the filling system, samples were withdrawn. Analytical verification consisted of determining the (b) (4) in (b) (4) and (b) (4) samples as well as determining (b) (4) in the (b) (4) samples with validated analytical methods.

Following the implementation of dedicated product contact equipment for filling, cleaning validation was performed as part of the re-qualification of filling line (b) (4) in 2010. Samples were collected from (b) (4). (b) (4) results provided for (b) (4) validation cycles including visual inspection after cleaning, (b) (4), and (b) (4), and dirty hold time. All test results met the acceptance criteria.

The (b) (4) procedure of the filling line is validated (b) (4) by (b) (4) to demonstrate homogenous and enough distribution of (b) (4)

For the last validation, (b) (4)

(b) (4)

Review comment: Filling line (b) (4) validation information found acceptable.

3.2.P.4 Control of Excipients

This section review differed to product reviewer.

Batch Numbering System:

In June 2014, the DP lot nomenclature changed once again to reflect the manufacturing process steps. The DP bulk lots were given a lot number starting with (b) (4) followed by (b) (4) and the packed DP lots were given a lot number starting with P followed by a 5-digit consecutive number (P00001).

This section review differed to product reviewer.

Hold Times:

(b) (4)

The storage and processing times are defined for the manufacturing process of the DP as shown in table below:

Hold Times during Drug Product Manufacture

Manufacturing step	Allowable
(b) (4)	(b) (4)
(b) (4)	
Hold time of final (b) (4) prior to filling	
Total manufacturing time (start filling until freezing)	
Freezing at (b) (4)	
Storage before sampling (-20°C)	

Review comment: The hold time information found to be acceptable as submitted and supported by hold time validation during process development/process validation or during media fill study.

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

Deferred to product reviewer and DBSQC reviewer of this file.

3.2.P.5.4 Batch Analyses

Verified the final drug product sterility, endotoxin, appearance results. All verified the sterilization and cleaning results (following the validated parameters).

3.2.P.5.5 Characterization of Impurities

Section review deferred to product office.

3.2.P.6 Reference Standards or Materials

Section review deferred to product office.

3.2.P.7 Container Closure System

Primary packaging components are constructed of the materials defined in Table below:

Table, Identity of Materials and Construction

Component	Description	Identity of material
Vial	2 mL	(b) (4) clear borosilicate glass
Stopper	13 mm grey rubber stopper	Bromobutyl compound with silicate filler (is made without natural rubber latex, chemicals associated with nitrosamines, di(2- ethylhexyl) phthalate or other phthalates or 2-mercaptobenzothiazole or any of its derivatives) (b) (4)
Cap	13 mm silver/yellow cap	Aluminum cap with polypropylene closure (flip tear up)

Shipping Validation

Shipment of temperature sensitive drug products is performed under controlled and validated conditions. MVA-BN DP is stored at -20°C ±5°C and shipments performed below -15°C.

DP is initially stored at the contract manufacturer (b) (4) and later (b) (4) for long term storage to BN-K. Validation information for cold storage at BN-K and transport to BN-K is provided . Additionally, information on shipment validation to customer locations like the United States Strategic National Stockpile (SNS) is included.

The shipment of MVA-BN DP from (b) (4) to SNS locations is performed with special containers, (b) (4)

Amount of (b) (4) used is calculated based on the desired temperature, product load and transport duration. The supplier has qualified

The performance and suitability of the (b) (4) container for deep frozen shipments was evaluated in two qualification tests. The ability of the container to maintain the product below -15°C under defined ambient temperature conditions was tested in a climate (b) (4) at the (b) (4) laboratory in (b) (4). The maximal ambient temperature in the climate (b) (4) was (b) (4)°C respectively (b) (4)°C.

The second qualification study was designed to stress the system and included ambient temperature profiles with extreme temperatures of (b) (4) °C. The product load was as described for the first qualification study, except that (b) (4)

(b) (4)

(b) (4) reported that during both studies, temperatures above -15°C were observed at certain locations on the pallets during the loading of the product into the container. However, product temperatures returned to below -15°C after approximately (b) (4). These results indicate that loading of the product is a critical step of the shipment process. As an additional step to decrease the possibility of temperature increases above -15°C, (b) (4)

(b) (4) This has been implemented for a mock shipment. Temperature mapping data showed that the product temperatures remained below -15°C during the transport from (b) (4) to the SNS location; however brief temperature spikes were again noted during loading of the pallets into the container for (b) (4) of the (b) (4) pallets, with temperatures returning to the specified temperature within (b) (4) after closure of the container doors. (b) (4) concluded that based on the results of the mock shipment and the container qualification regarding the temperature increasing during loading of the product, modifications to the loading procedure were implemented. The handling of the pallets during loading at (b) (4) was improved, including (b) (4)

(b) (4). The loading of the (b) (4) takes place in (b) (4) boxes which are easily placed onto the pallets. At the SNS site, (b) (4)

(b) (4) also performed simulated shipping conditions of the MVA-BN DP in the (b) (4) for potency and quality. Review of this will be deferred to the Product Office.

Shipment from (b) (4) to BN-K

Shipment is performed using refrigerated trailers by (b) (4). For the shipment validation, (b) (4), was performed. The acceptance criteria that the temperature recorded by each functioning thermocouple logger must be within -20°C ± 5°C had to be fulfilled during the validation.

(b) (4)

(b) (4)

(b) (4) stated that the shipment validation showed that the -20C refrigerated trailers met the acceptance criteria. (b) (4) performed additional shipment validation tests for the (b) (4) and (b) (4) times. (b) (4) also observed temperature loggers for (b) (4) for shipment of MVA-BN DP from (b) (4) to BN-K. (b) (4) reported all results met acceptance criteria. Two deviations were recorded: one occurred during loading of the trailer in an ongoing defrosting cycle. The other deviation was a temperature below -25°C due to malfunction of a controlling sensor. As a preventive action for the first deviation, loading of the trailer is avoided during the (b) (4) cycle.

Qualification of Cold Storage for MVA-BN DP at BN-K

DP is initially stored at the contract manufacturer (b) (4) and later (b) (4) for long term storage to BN-K. The cold store container was tested for (b) (4) under minimum load conditions to control the temperature within the required range of -20°C ± 5°C. A (b) (4) thermal mapping study was also performed under maximum load conditions during Performance Qualification (PQ). During PQ, door open recovery tests were performed for both doors, the main entrance at the front doors and the back doors. These tests were performed under minimum load conditions. For the qualification, thermocouple sensors were placed in (b) (4). (b) (4) sensors are positioned (b) (4). Figure X1 shows the cold store container with the main entrance, the back doors and the schematic sketched future pallet locations. The same sensor positions were used during the qualification with minimum and maximum load conditions. Additional sensors were used, in the (b) (4). In total (b) (4) thermocouple sensors were used during qualification.

In addition to the initial qualification, qualification under (b) (4) conditions were performed, as well as (b) (4) study. During these studies, the same (b) (4) temperature mapping and door opening tests were executed. During these studies the acceptance criteria were confirmed for the cold store container.

Review comment: *The shipment validation demonstrated that the -20C refrigerated trailers met the acceptance criteria. Temperature mapping data showed that the product temperatures remained below -15°C during the transport from (b) (4) to the SNS location, the shipping validation from (b) (4) to BN-K and met acceptance criteria, Shipping and cold storage qualification for the drug product at BN-K was performed and met acceptance criteria.. (b) (4) provided shipping and storage validation information and found acceptable.*

(b) (4) INFORMATION REQUEST:

Bavarian Nordic received a Request for Information regarding STN 125678/0 by Email on July 05, 2019. The information request concerned the (b) (4) facility. An extension of the original deadline from July 19th to July 31 was obtained.

CBER Question 1:

Regarding the HVAC system (section 3.2.A.1) that serve Building (b) (4) MVA-BN process areas, please provide following information:

- a) Total number of air handling units that serves the manufacturing areas.*
- b) Identification of each air handling unit that serves formulation buffer preparation, DS (b) (4), formulation, filling, stoppering, capping, sealing, and DS storage areas.*
- c) List of pressure differential ranges between different processing rooms in the manufacturing facility building (b) (4). Please describe containment feature for all open live virus vaccine processing areas.*
- d) Information on the HVAC validation history including initial qualification (time line when it was completed), list of critical parameters that were validated during qualification (please also cross reference STN number), most recent HVAC requalification validation summary report.*
- e) Regarding procedures and design feature to prevent contamination and cross contamination, please describe your product changeover procedures, open and closed procedures used, and airlocks used in different classification areas.*
- f) Provide a description of the routine monitoring program including frequency of monitoring (HEPA filter integrity, differential pressure, particulate level, temperature and humidity).*

Response Q1:

The total number of air handling units that serve the manufacturing areas in building (b) (4) is (b) (4) and (b) (4) air handling units that serve the manufacturing areas in building (b) (4) relevant for MVA-BN. An overview of the air handling units that serve the manufacturing areas for MVA-BN in building (b) (4) including identification, process steps and rooms is provided in table below.

Air Handling Units that serve the Manufacturing Areas for MVA-BN in Building (b) (4)

Process Step	Room(s) in (b) (4) Building	Air unit	Number of Air Handling Units
(b) (4)			

(b) (4)

Total number of air handling units that serve MVA-BN process areas in Building (b) (4)

(b) (4)

The room pressures and pressure differential ranges overview provided for the processing rooms in building (b) (4). (b) (4) explained that the only open virus step during process is the (b) (4) step. The filling and stoppering containment feature include (b) (4)

(b) (4). Hepa filter air at supply and exhaust, and grade (b) (4) condition for filling and stoppering.

Pressure Differential Ranges in Building (b) (4)

Room in Building (b) (4)	Room Pressure	Pressure Differential to outside Building (b) (4)	Activity/Purpose
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(b) (4)

An overview of the qualification documentation for the HVAC system is provided in Table below. Critical parameters that were monitored including (b) (4) HVAC system qualification was performed in 2016.

Qualification Overview HVAC System

Qualification Phase	Document No.	Date of Completion
DQ	QB_DQ_312.04_V001	13-Jul-2015
IQ/OQ	QB_IQ-OQ_312-KB 30.01_V001	19-Aug-2015
PQ	QB_PQ_312-KB 30.02_V001	23-May-2016

Critical Parameters:

(b) (4)

Prevention of cross contamination include implementation of product changeover procedures, use of open and closed procedures, airlocks used in different classification areas for the two manufacturing activities. Filling system and formulation vessels are cleaned and sterilized by (b) (4) production (user manual UM-000031 , WI-OOOI 17) . Inactivation of product-touched parts after production (as per WI-000090 , P-HAL234) All product-contacting equipment is used as product-specific dedicated equipment, equipment are autoclaved (b) (4) and (b) (4) of the production area (room (b) (4)) after last production.

HEPA Filter integrity is carried out in cleanroom class (b) (4) and class (b) (4) and in class (b) (4) . Differential pressure, temperature, pressure and humidity are recorded and monitored continuously via central building control systems. Warnings and alarm limits are automatically generated GMP-critical alarms go to the cell phone of an emergency service . In the process room for filling of drug product, particles of sizes (b) (4) are measured continuously in cleanroom class (b) (4) with measuring points in class (b) (4) and (b) (4) in class (b) (4) .

Review Comment: (b) (4) provided requested information regarding the AHU units, pressure differential ranges between different processing rooms, HVAC validation history, most recent requalification summary, prevention of cross contamination, and HEPA filter routine monitoring procedures and found acceptable.

CBER Question 2

Regarding your Environmental monitoring program (section 3.2.A.1.2.3):

- a) Please provide a description of the routine and batch related EM program including frequency of monitoring, sampling locations, alert and action limits.*
- b) Please provide an environmental monitoring test results for the conformance batches (2014) and summary test results for the media fill batches (most recent media fill for line (b) (4)) including list of EM deviations, root cause analysis and*

corrective and preventive action taken.

- c) *Please provide environmental monitoring performance qualification (EMPQ) summary and test results the filling line (b) (4) (grade (b) (4) and Grade (b) (4) areas). (note - study performed for the clean rooms to demonstrate environmental control can be maintained under static and dynamic condition)*

(b) (4) Response:

(b) (4) provide a summary of the routine and batch related EM program including frequency of monitoring, and alert/action limits is provided in table below:

Parameter	Batch-related EM Program	Routine EM Program
Frequency	For every produced batch	(b) (4) if no production took place
EM Methods and Sampling	(b) (4)	
Sampling locations	Defined in document VI-000069	Defined in documents VI-000072 and VI 000073
Limit	Defined in SOPT-000020	Defined in SOPT-000020

The environmental monitoring test results during manufacture of the conformance batches 2014 (#(b) (4)) are provided. The results of all (b) (4) batches met the requirements of the SOP valid at the time of production. There were no EM deviations during production of the (b) (4) conformance batches 2014.

The environmental monitoring results obtained during the most recent media fill for filling line (b) (4) performed in January 2019 are summarized. For the viable monitoring, no warning or action values were exceeded. Most results were equal to (b) (4). The environmental monitoring results (b) (4) were observed during the preparation of (b) (4), the formulation at filling line and filling process.

During the preparation of (b) (4), the microbiological clean room monitoring in the locks was missed. This fact was evaluated in the deviation report DEV-19-0138. For the particle monitoring, there was only one value exceeding the warning or action value as listed in Table 13. This exceedance was evaluated in the deviation report DEV-19-0036 (see Table 14). The missing new clean room monitoring was due to insufficient communication between the in-process control (IPC) team and the formulation staff with

regard to particularities of this sampling (re-sampling). As a corrective action, the formulation staff was given training regarding clean room monitoring of locks at media fill.

(b) (4) provided following four reports for environmental monitoring performance qualification (EMPQ) summary and test results for the filling line (b) (4) (grade (b) (4) and Grade (b) (4) areas):

- 02c_PQ_(b) (4) _27-04-2009_08_SB Vers.002
- 02c_PQ_(b) (4) _RRM L. 6 Geb 312_14-04-2009_10_SB
- 02c_P-UB-00395.00-V001
- 02c_P-UB-00405.00-V002

All acceptance criteria were met, and study demonstrated that environmental control was maintained under static and dynamic conditions.

Review Comment: (b) (4) provided EM program detail including routine/dynamic EM monitoring frequency, sampling locations and alert and action limits. In addition, provided information on EM test results for conformance lots and EMPQ summary test results for the filling line (b) (4). (b) (4) provided response is acceptable.

CBER Question 3

Regarding Production area Sanitization (section 3.2.A.1, 7.4):

- List of validated cleaning disinfection agents.*
- Validated contact times and cleaning disinfection agent concentration.*
- Cleaning and disinfection agent effectiveness summary.*

Response Question 3

A list of the validated cleaning disinfection agents used in the production area during manufacturing including the validated contact time and cleaning disinfection agent concentration provided as follow:

Name	Used for	Application (Concentration/Time)	Efficacy
For Cleanroom class (b) (4)			
Perform sterile concentrate (b) (4)	-after contamination/spill -disinfection after production -disinfection after (b) (4)	(b) (4)	Partially virucidal*, bactericidal, sporicidal
(b) (4)	-disinfection after (b) (4)		bactericidal, sporicidal
(b) (4)	-disinfection after (b) (4)		bactericidal
(b) (4)	-Hand disinfection		bactericidal
Surrounding rooms in cleanroom class (b) (4) (e.g. airlocks)			

(b) (4)	-disinfection after (b) (4)	(b) (4)	bactericidal, sporicidal
	-disinfection after (b) (4)		bactericidal, sporicidal
	-disinfection after (b) (4)		bactericidal
	-disinfection after (b) (4)		Bactericidal

Microbicidal Efficacy

Representative surfaces were defined based on a risk analysis (Q-RA-02611.00-V001) in which clusters were formed based on physico-chemical properties. The worst case for each cluster was identified (criteria: (b) (4))

and used for validation. Validation was carried out according to (b) (4)-guidelines. For non-sporicidal disinfectants, (b) (4)

are employed. Sporicidal disinfectants are additionally challenged against spores of (b) (4) and against an in-house isolate of gram-positive spore formers.

Acceptance criteria met for a log reduction of (b) (4) log against vegetative forms and (b) (4) log against spores.

Virucidal disinfectants were validated according to the guideline from (b) (4) from 1995, supplemented with the (b) (4) guideline from 2015 in a quantitative carrier test. Disinfectants are challenged with enveloped and non-enveloped viruses; acceptance criterion is a log reduction of (b) (4) log. If a disinfectant can only inactivate enveloped viruses, it is marked as "partially virucidal" and may only be used for the decontamination of enveloped viruses.

The validated (b) (4) agent used for facility (b) (4) in building (b) (4) is (b) (4). Evaluation of effectiveness of the (b) (4) agent (b) (4) was demonstrated according validation plan P-UP-00336.00-V001 by inactivation (b) (4) log reduction) of (b) (4) bio indicators which were distributed on the filling area line (b) (4) in building (b) (4) (in rooms (b) (4))

Review Comment: (b) (4) provided requested information including the list of validated disinfection agents, validated contact times and disinfection agent concentration. The disinfection effectiveness study demonstrated adequate log reduction for the challenged test virus. (b) (4) response is acceptable.

CBER Question 4

Regarding equipment list provided in Table 4 and table 5 (section 3.2.A.1):

Please provide a brief equipment qualification summary for the (b) (4), washing machine, autoclave and sterilization tunnel. (clarification

note – verify that IQ and OQ was completed and provide summary of significant tests performed during OQ/PQ and results)

Response Question 4

A summary of the equipment qualification activities for the (b) (4) washing machine, autoclave and sterilization tunnel was provided as follow:

(b) (4) :

- Equipment-no.: (b) (4)
- Initial qualification approved: 26.10.2006,
- Reports: PQ_VM 00 37_26-10-2006_02_SB, PQ_VM 00 22_26-10-2006_02_SB;
- DQ, IQ, OQ-tests included:
 - completeness and intactness of delivered, installed components,
 - maintenance,
 - SOPs and their training,
 - Calibration of temperature measurement,
 - functional testing of protection measure and alarms ((b) (4) process interrupted/ (b) (4) process can be restarted),
 - power breakdown,
 - (b) (4) tests: (b) (4)
 - (b) (4) of tubing,
 - media transfer,
 - detection of coded tube holding,
 - printer test

Results: all tests fulfilled the acceptance criteria

(b) (4) :

IQ,OQ, PQ was completed on June 2016.

DQ, IQ, OQ, PQ-tests included:

- existence specification of incoming goods inspection,
- delivered and installed components,
- SOPs and their training,
- functional testing of ports,
- functional testing of sterility and
- process sequence

Results: all tests fulfilled the acceptance criteria

Washing Machine:

Qualification included:

- functional testing of alarms,

- emergency stops
 - calibration of temperature sensors and (b) (4) ,
 - tolerance conductance value,
 - control of temperature points of calibration
- Software was updated in 2011 according to technical change
 - Results: all tests fulfilled the acceptance criteria
 - Last periodic review: BW_WM 800 09_WM 800 10-V002 approved: 18.11.2014

Autoclave

Initial qualification was approved on March 2010

OQ/PQ-tests included:

- Calibration of temperature and pressure sensors
- (b) (4) Test,
- Item (b) (4)

Results: all tests fulfilled the acceptance criteria

Sterilization Tunnel (included in the total filling line (b) (4) system)

(b) (4)

Review Comment: (b) (4) provided equipment qualification summary for the (b) (4) , washing machine, autoclave and sterilization tunnel and found adequate. (b) (4) performed autoclave and depyrogenation cycle validation for different loads in separate studies, these reports were reviewed during PLI or as part of BLA review.

CBER Question 5

Regarding sterilization of container closure (section 3.2.P.3.5, section 3.1), Please provide following (most recent validation performed) including study date, number of runs;

- a) *Please provide, vial cleaning validation report including washing test parameters monitored, acceptance criteria, test results and list of deviation and resolutions.*
- b) *Please provide, vial depyrogenation validation report including parameters monitored, acceptance criteria, test results and list of deviation and resolutions.*
- c) *Please provide, stoppers sterilization validation report including parameters monitored, acceptance criteria, test results and list of deviation and resolutions*

Response Question 5:

A summary of the vial cleaning validation report is provided below. The translated report is provided as follow:

Validation documentation:

- Validation plan P-VP-01447.00-V001 approved on: 12.01.2017
- Validation report P-VB-01447.00-V001 approved on: 05.07.2017

Monitored parameters:

(b) (4)

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Acceptance criteria:

(b) (4)

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Test results:

(b) (4)

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List of deviations and resolution:

- No deviation

A summary of the vial depyrogenation validation report is provided below. The translated report is provided as follow:

Study date, number of runs

- Last validation: 11.03.2019, (b) (4)

Validation documentation:

- Vial depyrogenation validation report SM_(b) (4)_07-01-2019_TP_SB, approved: 10.04.2019

Monitored parameters:

(b) (4)

Acceptance Criteria:

(b) (4)

Test results:

- Successful completion of (b) (4), without deficiency
- Line (b) (4) still approved for production
- All acceptance criteria passed

Deviations:

- There was one deviation only: DEV-19-0271 – Sterilization failed due to failed measurement of (b) (4) thermocouples
- Root cause: Handling error of the measuring equipment by validation staff
- Correction: rerun (successful)

A summary of the stoppers sterilization validation report is provided below. The translated report is provided.

Equipment: Autoclave (b) (4)

- Program 1
- Steam sterilization
- Sterilization temperature: (b) (4)
- Sterilization time: (b) (4)

Study date, number of runs

- Last validation in 2019: (b) (4) performed on 12.03.2019
- Validation report in drafting

Acceptance criteria

- (b) (4)

(b) (4)



Test results

- In all revalidation runs of the (b) (4) it was proven that program 1 is effective against microbiological loads and provides reproducible results.
- The required sterilization temperature of (b) (4) was maintained for the required period of (b) (4) at all internal temperature sensors as well as at all additional used sensors.
- The evidence of sterility provided by the (b) (4) could be objectively demonstrated. The positive control shows growth.

Deviation:

2019 deviation for the failure logger, not critical, logger was not evaluated (according to WI-000485 V3.0), no critical position

Review Comment: (b) (4) provided information on vial cleaning validation, vial depyrogenation validation, and stoppers sterilization validation and provided information found adequate. Response is acceptable.

CBER Question 6

Regarding qualification and sterilization of formulation vessel (section 3.2.P.3.5):

- Please provide most recent (b) (4) requalification summary including parameters monitored, acceptance criteria, test results and list of deviation and resolutions

Response Question 6:

A summary of the most recent (b) (4) requalification is provided below:

(b) (4) vessel (dedicated):
P-UB-00551.00-V001, approved: 09.07.2010

- dedicated cleaning-validation for (b) (4) vessel (cleaning group (b) (4))
- Results: dedicated (b) (4) vessel: (b) (4) runs without any deviations, all results met the defined acceptance criteria
- Deviations: no deviations

For small and large vessels:

P-VB-00011.05-V001, approved: 29.05.2018

- validation for all standard cleaning groups (included (b) (4))
- results: routine (b) (4) -station validation (small and large vessels) one (b) (4) for each vessel group, effectiveness of the cleaning processes could be proven,
- two deviations: DEV-17-1540 (exceeding VMP validation master plan - interval. All cleaning processes must be regularly revalidated, which is why the cleaning of the (b) (4) containers on the (b) (4) -station must be revalidated every (b) (4). Time overrun for processing due to lack of personnel) closed on 13.05.2018, DEV-18- 0271(exceedance of acceptance limit on one measuring point due to procedural error that does not occur in the routine this way) repetition of the run was successful without any deviation

For both (b) (4) validations, dirty and clean hold time was monitored. Last (b) (4)

Acceptance criteria

(b) (4)

(b) (4) Vessel (b) (4):

Validation Runs for (b) (4) Vessel

(b) (4)

(b) (4)

(b) (4)

Acceptance criteria:

(b) (4)

Test results

All acceptance criteria were met, there was no growth in the (b) (4) used/ positive controls outgrow, the required sterilization temperature and time was maintained. One deviation noted as follows:

DEV-19-1151 (only for the (b) (4) vessel, incorrect positioning of the temperature sensor for validation run) repetition of the run was successful without any deviation.

Review Comment: (b) (4) provided (b) (4) validation summary for the formulation vessels and found adequate. Response is adequate.

CBER Question 7

Regarding Autoclave validation (section 3.2P.3.5):

- a) Identify the autoclave(s) used including manufacturer and model number.
- b) Describe autoclave sterilization process (cycle type, list of different loads qualified, number of minimum/maximum loads qualified).
- c) Please provide the most recent sterilization revalidation test results for the process equipment and (b) (4) including number of runs performed, number of (b) (4) used, F0 value achieved for each location, (b) (4) test results, (b) (4) D value and concertation used, list of deviation and resolutions.
- d) Describe methods and controls used to monitor routine production cycle (for all validated autoclave loads).

Response Question 7

The autoclave used for MVA-BN has the internal equipment number (b) (4). The manufacturer of the autoclave is (b) (4). The serial number is (b) (4).

Preconditions for autoclave revalidation:

(b) (4)

Revalidation of the programs – Acceptance criteria

(b) (4)

(b) (4)

Minimum/maximum loads:

- Minimum load is tested only in initial validation
 - (b) (4) runs for initial validation
- Revalidation with maximum load ((b) (4))
- The maximum load includes critical items (worst case loading) according to the risk analysis (current) P-RA-00549.00-V008
- (b) (4) , fully loaded with critical production equipment according to worst case loading program 8 (dedicated),

Most recent revalidation result:

The most recent sterilization revalidation was conducted in 2019. Normally a revalidation is done with (b) (4) , but due to a technical change the revalidation included (b) (4) runs.

Each run included (b) (4) and (b) (4) pressure sensor per run. The (b) (4) with a concentration of (b) (4) and a (b) (4) value of (b) (4) . All runs showed (b) (4) . The F0 value at all locations was (b) (4) (acceptance criteria (b) (4)). There were no deviations during the revalidation in 2019.

Routine cycle - control

The manual loading of the autoclave is regulated in work instruction WI-000116. It specifies on which layers and in which amount the equipment can be sterilized. The sterilization process itself is monitored by means of internal pressure and temperature sensors. These are used to control the program. Based on defined and validated limit values, a fault would be triggered in the event of a deviation. This is noted on the batch protocol and would be noticed by the shift management during the check. In this case an evaluation of the fault is necessary. Program parameters are time (b) (4) and temperature (b) (4) . The autoclave processes are revalidated (b) (4) by (b) (4) . All other qualification-relevant data is checked (b) (4) during the periodic review. (b) (4) , a (b) (4) test is carried out to check the leak integrity of the system. The tracking takes place via the VMP in SAP.

Review Comment: Response is acceptable. (b) (4) provided autoclave cycle validation for the process equipment and (b) (4) and found adequate.

CBER Question 8

Regarding Filling line (b) (4) validation (section 3.2.P.3.5), Please provide following:

- a) (b) (4) validation study timeline (study performed date)
- b) (b) (4) acceptance criteria and test results
- c) (b) (4) value and concentration used
- d) List of deviation, identification of probable root cause, and corrective and preventive actions taken.

Response Question 8

The (b) (4) process of the filling line is revalidated (b) (4) with (b) (4). The last revalidation was performed on 25-Jun-2019. There were no deviations during the revalidation in 2019. The (b) (4). The (b) (4) used had a population of (b) (4) and a (b) (4). The (b) (4) cycle demonstrated adequate sterility assurance.

Review Comment: Response is acceptable. (b) (4) provided additional detail for the Filling line (b) (4) validation for the (b) (4) used, acceptance criteria and test results.

CBER Question 9

Regarding (b) (4) of the (b) (4) vessels (Section 3.2.P.3.5)

- Please provide actual test results (numerical value) for acceptance criteria provided in the table #42 and Fo value for the locations monitored (figure 15).
- In addition, provide the D value and concentration for the (b) (4) used for the (b) (4) study, validated clean and dirty hold time for the (b) (4) cycle and sterilization hold time for the sterilized equipment.
- Regarding (b) (4) study for the filling line# (b) (4) and (b) (4) tank, please describe how (b) (4) cycle was validated for the worst-case product removal?

Response Question 9

Actual Test Results for Acceptance Criteria

(b) (4)

Note : for Vessel (b) (4) was not reported, however all (b) (4) acceptance was met and did not ask for actual value.

Worst case – (b) (4) vessels:

Based on the worst-case assessment, (b) (4) sizes of the (b) (4) vessels were chosen for validation: (b) (4). (based on volume, complexity, cold points, number of nozzles, sensors fitting).

(b) (4) used for the last (b) (4) Revalidation

- (b) (4)
- Population: (b) (4)
- (b) (4)

The F_{real} value for monitored locations are provided in the following tables. The F_{real} value indicates how long it takes to reach SAL of (b) (4). (maximum value reported for F_{real} was (b) (4) vessel, minimum value of (b) (4) recorded for vessel (b) (4)).

Maximum (b) (4) was established for the Sterilization hold time.

Filling line (b) (4)

Documentation

- a) Recent validation plan: P-VP-00003.06-V001, released on: 22.08.2016
- b) Recent validation report: P-VB-00003.07-V001, released on: 24.07.2018

Parameters Monitored:

(b) (4)

Acceptance criteria

(b) (4)

Review Comment: (b) (4) provided adequate information for the (b) (4) vessels. Response is acceptable.

CBER Question 10

Regarding your Water for injection system:

- a) *How many drops does the system have?*
- b) *How often is the WFI system tested for (b) (4) ?*
- c) *Please provide the acceptance criteria for (b) (4)*

Response 10:

There are two water systems in Building (b) (4). The (b) (4)-System and the WFI system. The sampling points, tests, test frequencies and acceptance criteria for the water systems are summarized as follow:

Water System	Sampling Points	Tests	Frequency	Acceptance Criteria
(b) (4) - System	(b) (4)			
WFI-System				

The (b) (4) is not measured in the WFI system since the WFI is circulated in this system at (b) (4). There is no further measurement afterwards.

Review Comment: Response is acceptable. (b) (4) provided additional information regarding WFI system including acceptance criteria, test frequencies and number of user points and found adequate.

CBER Question 11

Regarding your other product contact utilities (for example (b) (4)), Please describe number of drops that provide these utilities to production areas. Please describe routine monitoring performed (tests performed, acceptance criteria and frequencies).

Response:

The sampling points, tests, test frequencies and acceptance criteria for the other utility systems are summarized as follow:

(b) (4)

(b) (4)

Review Comment: Response is acceptable. (b) (4) provided additional information for the (b) (4) and found acceptable.

CBER Question 12

Regarding Computer system, please provide a summary of the general description of computer systems which control critical manufacturing processes including validation summary and change control procedure.

Response:

A summary of the general description of computer systems which control critical manufacturing processes is provided as follow:

(b) (4)

Revalidation summary

(b) (4)

Review Comment: Response found adequate. (b) (4) provide the computer system validation summary and found acceptable. All changes were performed following the change control procedure.

CBER Question 13

Please provide the details and results of filling process (critical parameters) that were monitored during filling of conformance lots (i.e. weight checks, fill uniformity, time of fills etc.), and the acceptance criteria, that ensure consistency in the filling process. Please provide filling consistency (weight check) validation summary.

Response:

Critical process parameters and results of the filling process during filling of the conformance lots 2014 is provided as follow:



On filling line ^{(b) (4)}, automated in-process control (IPC) fill weight is performed using ^{(b) (4)} on a subset of filled vials. Each of the ^{(b) (4)} filling pump positions is sampled successively. The fill weight limits are applied for this product: Mean fill volume = ^{(b) (4)}
Warning limit = ^{(b) (4)}.

No fill weight action limit deviations occurred during production of the ^{(b) (4)} validation batches in 2014. No statistically significant difference over the course of formulation and filling was observed for virus titer, total protein and genomic quantified MVA-BN DNA. These data support that the filling process results in a homogeneous product.

Review Comment: Response is acceptable. ^{(b) (4)} provided the filling process critical parameters that were monitored during the conformance runs including the weight check and found met acceptance criteria.

CBER Question 14

Regarding Media fill, please provide media fill study protocol and summary reports for last ^{(b) (4)} media fills performed (line #^{(b) (4)}, building ^{(b) (4)}). For each media fill results, please include information on worst case conditions used, container/closure used, media used, number of units filled, units ^{(b) (4)}, units discarded before and after ^{(b) (4)}, positive units used, ^{(b) (4)} parameters, date of the media fill study performed, duration of each media fill run, batch size comparison to production, type of interventions used, total number of operators participated.

Response Question 14

The last (b) (4) media fills were performed in (b) (4)
[REDACTED]. A summary of the data is provided.

(b) (4)

(b) (4)

Review Comment: Response is acceptable. (b) (4) provided last (b) (4) media fill test results and found provided information adequate.

CBER Question 15

Regarding your semi-automated Visual Inspection Process:

- a) Please provide the (b) (4) inspection machine qualification report (verify that IQ was completed, qualification summary and results of key process parameters during OQ and PQ).*
- b) Please provide inspection process reject rate limit, and action taken when the reject rate is exceeded.*
- c) For semi-automated visual inspection, what are the qualification requirements and frequency.*
- d) Please provide visual inspection results for the 2014 process validation runs*

Response Question 15

There are (b) (4) inspection machines:

(b) (4)

IQ:

IQ consists of tests like SOP, training, identification, log book, maintenance, check of installed systems, check of delivered documentation.

OQ consist of functional tests:

(b) (4)

No deficiency during IQ/OQ.

The inspection process reject rate limit is (b) (4). When the reject rate is exceeded, a deviation will be opened.

The following qualification requirements are defined in the specifications:

(b) (4)

The following periodic actions for the visual inspection machines are defined:

(b) (4)

Visual inspection results for the process validation runs 2014 are summarized as follow:

Batch	
Total rejects	
Discard because of breaking	
Discard to be classified	
Critical	Cracks
	Air lines
	Stopper missing
	Incomplete capping
Major	Glass failure – inclusions
Minor	Glass failure – scratches, impurities
	Small bumps/ checks in caps
	Over-/underfills, empty vials
	No turbidity/ clear solution
	Particles non-product related, dust, glass, particles (b) (4)

(b) (4)

Review Comment: Response found adequate.. (b) (4) provided visual inspection information including machine qualification, reject rates and process validation runs visual inspection results and found acceptable.

CBER Question 16

Regarding your final product labeling process:

- a) Please describe your labeling process (labeling areas, equipment used, inventory control, mix up prevention, accuracy)*
- b) Please provide labeling machine qualification report (verify that IQ was completed, qualification summary and results of key process parameters during OQ and PQ)*

Response Question 16

The machine for the labelling of the vials is placed in building (b) (4) in line (b) (4). The line (b) (4) is situated in a controlled but not classified environment with temperature control between (b) (4). The line (b) (4) contains also a (b) (4) for sub-sequent processes after labelling.

The machine was installed in 2006 and has an (b) (4). The variable data on the adhesive label are printed by the machine on the label. Besides the check for correct printed variable data, the identity of the adhesive label is also checked. Furthermore, the presence of the adhesive label on the vial is checked during labelling. Before start and before end of labelling process, the control facilities are checked for correct operation, which is documented in the batch record. Additionally, regular in-process controls are performed to check the machine for correct operation. During those in-process controls the print on the adhesive labels; the correct placement / position on the vial and the identity of the adhesive label are proven.

When receiving packaging materials, the materials are booked under a specified SAP material number and a new generated SAP batch number in the warehouse. After sampling and incoming goods check, the material is released for production. The adhesive labels have a back-side- number, ensuring the correct counting. The starting number and the end number on the carrier tape are documented in the batch record ensuring the correct reconciliation. Residual amounts of unprinted adhesive labels on the role can be brought back into the warehouse and are booked in SAP (amount and storage place connected to SAP batch and material number). The number of adhesive labels stored can be verified by the numbering on the carrier tape. The reconciliation of bulk material and packaging materials is described in WI-000133.

Mix up prevention including line clearance, reconciliation of all materials, identification of materials and material secured in locked cages.

All qualification phases were completed; expected machine performance has been verified ((b) (4) vials/hour). Performance of the packaging line was performed and consists of verification using an AQL-based test scenario with (b) (4) Imvamune (JYNNEOS) batches

Item	Test performed	Acceptance Criteria met	Result
Visual inspection	(b) (4)	Yes	No difference between inlet and outlet* rejected vials
		Yes	(b) (4)
		Yes	0 defects
Labelling machine		Yes	Any vial with wrong label was rejected

Item	Test performed	Acceptance Criteria met	Result
	(b) (4)	Yes	Any vials with altered data was rejected
		Yes	All vials w/o labels were rejected
		Yes	(b) (4)
		Yes	All incompletely filled blisters were rejected
Cartoning machine	(b) (4)	Yes	All boxes with altered identification were rejected
		yes	No difference to manual control
		Yes	Accountability of (b) (4)
Control weigher	(b) (4)	Yes	All defective folding boxes were rejected
		Yes	Defective boxes were rejected
		Yes	All inspections passed

Review Comment: (b) (4) provided adequate description of the labeling process and verified the labeling equipment qualification status. Response is acceptable.

CBER Question 17

Regarding drugs substance storage area:

- Please provide brief description of DS storage procedure at (b) (4)
- Please provide qualification summary for the (b) (4) that use for DS storage
- Describe routine monitoring of DS storage area and how temperature alarms are monitored and responded.

Response Question 17

The Drug Substance (DS) is delivered from the Bavarian facility in Kvistgaard, Denmark and stored in (b) (4) building (b) (4) in a dedicated storage room maintained at (b) (4). The (b) (4) storage room is qualified, and the temperature is permanently controlled as all temperature sensors connected to the Building Management System (BMS). In case of temperature excursions, a 24/7 alarm response team is established.

DS delivered from Bavarian facility in Kvistgaard, Denmark will be stored in (b) (4) warehouse building (b) (4) in dedicated (b) (4) maintained at (b) (4). Warehouse building (b) (4) is permanently locked and access controlled. Only authorized operators have access to the building. Room (b) (4) as well as the (b) (4) are qualified; temperatures are controlled and continuously monitored as all temperature sensors are connected to the Building Management System (BMS). If temperature excursions occur, an on-call service (24/7) is in place. Any movement of material containers from one storage place to another requires an approved SAP transport order

Summary of Qualification performed:

IQ: it was confirmed that the (b) (4) are completely installed, according to their specification

OQ: Proper functionality of all components of the (b) (4) were confirmed.

PQ: evidence was documented that the (b) (4) meet the required specification of (b) (4). The connection to the PIS system was performed and qualified within the PQ-phase after the determination of (b) (4) for the position of permanently installed PIS sensors(s). (b) (4)

The (b) (4) storage room in building (b) (4) used for storage of MVA-BN DS is qualified and the temperature is permanently controlled as all temperature sensors are connected to the Building Management System (BMS). The sensor positions were determined during the qualification of the building (temperature mapping). The performance of the warehouse is documented in (b) (4) warehouse reports and reviewed by the management. If a temperature approaches a limit value, a warning is issued to the logistics management. In case of temperature excursions, a 24/7 alarm response team is established. The building (b) (4) is connected to a dedicated backup power system which is periodically tested.

The (b) (4) located in in warehouse building (b) (4) used for storage of MVA-BN DS are qualified; temperatures are controlled and continuously monitored as all temperature sensors are connected to the Building Management System (BMS). Temperature sensors positions are based on the outcome of the re-qualification. According to (b) (4) Standard Operating Procedure SOP-000073 (Warehouse rules), a (b) (4) evaluation and trending of temperatures is performed. Alarm messages are alerted to the warehouse management as well as to the operators of the on- call service. After consultation between the warehouse management and the operators of the on- call service, a decision on how to solve the cause of the alarm is to be made. Alarm messages showing temperature deviations are to be documented and evaluated via deviation report.

Review Comment: (b) (4) provided DS storage description, (b) (4) qualification summary and routine procedural control and found adequate. Response is acceptable.

CBER Question 18

Regarding drugs substance storage area:

- a) *Please provide brief description of DP storage procedure at (b) (4)*
- b) *Please provide qualification summary for the freezer (freezing (b) (4)) that use for DP storage*
- c) *Describe routine monitoring of DP storage area and how temperature alarms are monitored and responded*

Response Question 18

The DP finally packaged is put into shipping cartons and placed on pallets according to defined packaging pattern. DP is then moved from the packaging department in building (b) (4) to building (b) (4) for the freezing and storage (-20 °C) steps:

The following points were tested successfully, documented in the Testo qualification documentation (PQ 2 folder), and released on 15 November 2011:

- Documentation of the test media employed for measuring the temperature distribution
- Documentation of the measuring point distribution
- Verification of the local and time-related distribution of the temperature with load (b) (4)
- Verification of the local and time-related distribution of the temperature inside test substance incl. worst-case load inside (b) (4) freezer
- Door opening test
- Power failure test with load

The Performance Qualification was concluded without existing deficiencies.

The -20°C storage room in building (b) (4) used for storage of MVA-BN DP is qualified and the temperature is permanently controlled as all temperature sensors are connected to the Building Management System (BMS). The performance of the warehouse is documented in (b) (4) warehouse reports and reviewed by the management.

Review Comment: Response is acceptable. (b) (4) provided drug product storage description, equipment qualification summary and routine procedural control found acceptable.

CBER Question 19

Regarding DS (b) (4) equipment, please provide qualification summary for the (b) (4) that are used for DS (b) (4).

Response Question 19

Incubator qualification summary provided as follow:

(b) (4) :

(b) (4) , Equipment-no.: (b) (4)

Initial qualification approved: 29.05.2018

Qualification Documentation QB PQ_1009767 V002

DQ IQ OQ PQ-tests included:

- completeness and intactness of delivered, installed components,
- connection to the BMS (building management system),

- maintenance,
- SOPs and their training,
- calibration,
- functional testing of protection measure and alarms,
- (b) (4) measurements in loaded and unloaded state for (b) (4),
- definition of (b) (4) for continuous monitoring
approved: 25.10.2018 (QB PC 1009767.01)
- (b) (4) measurements in loaded state for (b) (4), door opening tests
- Extract from qualification test, (b) (4) provided in Figure 14.

(b) (4) Qualification summary:

Equipment ID:

(b) (4) : Equipment-no.: (b) (4)

Initial qualification approved: 22.05.2015

DQ IQ OQ PQ-tests included:

- completeness and intactness of delivered installed components,
- connection to the BMS (building management system),
- maintenance,
- SOPs and their training,
- calibration,
- functional testing of protection measure and alarms,
- (b) (4) measurements in loaded and unloaded state for (b) (4)
- definition of (b) (4) for continuous monitoring
- First Requalification approved: 17.12.2018
- (b) (4) measurements in loaded state for (b) (4), door opening tests

All other refrigerators were qualified and found acceptable.

Review Comment: Response is acceptable. (b) (4) provided (b) (4) qualification summary found acceptable.

CBER Question 20

Regarding Formulation Buffer preparation step

- Please provide (b) (4) limit. Provide (b) (4) results for conformance lots.
- Please provide (b) (4) validation (b) (4) study) summary

Response Question 20:

The formulation buffer (10 mM Tris, 140 mM NaCl, pH 7.7) is (b) (4)

(b) (4)

Review Comment: Response is acceptable. (b) (4) provided formulation buffer (b) (4) control acceptance criteria and (b) (4) study summary and found acceptable.

CBER Question 21

*Regarding container closure method used:
Please provide a description of your CCIT (b) (4) test Methods outlining all steps and parameters used (including positive control used, worst case conditions and limit of detection).*

Response Question 21:

The container closure integrity (CCI) tests were performed using the (b) (4) test and (b) (4) tests.

(b) (4) test (CCI)

The CCI analysis of the IMVAMUNE® Container Closure System was performed using (b) (4)

(b) (4)

(b) (4) test (CCI)

(b) (4) test was performed in 2008. Following container closure systems were tested:

Vial	Stopper	Caps
Vial-(b) (4): 2 mL, (b) (4)	Stopper-(b) (4): 13 mm bromobutyl injection rubber stopper, (b) (4)	13 mm silver/yellow aluminum cap, (b) (4)
Vial-(b) (4): 2 mL, (b) (4)	Stopper-(b) (4): 13 mm bromobutyl injection rubber stopper, (b) (4)	(b) (4)
Vial-(b) (4): 2 mL, (b) (4)	Stopper-(b) (4): 13 mm bromobutyl injection rubber stopper, (b) (4)	13 mm silver/yellow aluminum cap, (b) (4)
Vial-(b) (4): 2 mL, (b) (4)	Stopper-(b) (4): 13 mm bromobutyl injection rubber stopper, (b) (4)	(b) (4)

(b) (4)

The test did not indicate any differences in integrity among the different closure systems.

Review Comment: Response is acceptable. (b) (4) provided drug product CCIT (b) (4) test found acceptable. (b) (4) tested all vials crimped a both (b) (4) passed the (b) (4) rate at all temperature conditions.