



**To:** File, Original Biological License Application (BLA) STN 125694/0

**From:** Wei Wang, CMC & Facility Reviewer, Lead Inspector, OCBQ/DMPQ/B1

**Through:** Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1

**CC:** Deborah Trout, Consult Reviewer, Inspector, Team Lead, OCBQ/DMPQ/B1  
Amanda Trayer, DMPQ RPM, OCBQ/DMPQ/ARB

**Subject:** DMPQ Review Memo for the BLA, STN 125694/0

**Applicant:** AveXis, Inc. (US License No. 2104)

**Product:** AVXS-101 (onasemnogene abeparvovec, ZOLGENSMA), general information:

- a. The pharmacological category: A gene therapy biological product, consisting of a non-replicating recombinant adeno-associated viral vector serotype 9 (AAV9) containing the human Survival Motor Neuron (SMN) gene under the control of the cytomegalovirus (CMV) enhancer/chicken- $\beta$ -actin-hybrid promoter (CB).
- b. Dose form: A sterile solution of  $2.0 \times 10^{13}$  vector genomes (vg)/mL.
- c. Strength:  $1.1 \times 10^{14}$  vg/kg (body weight)
- d. Route of administration: Intravenous (IV) infusion
- e. Indication: For the treatment of pediatric patients with spinal muscular atrophy (SMA) Type 1 with or without disease onset.

**Facility:** AveXis, Inc. (b) (4) (The main facility where the manufacture of drug substance and drug product, various analytical tests and storages are performed)

**Due Date:** June 01, 2019

**Recommendation:** Approval of this BLA is recommended

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## SUBMISSIONS REVIEWED

Submissions under the DMPQ purview per the CBER SOPP 8401.4 were reviewed and covered in this memo (prepared by following the CBER T846.04).

Date Received	Submission STN	Comments/Status
10/03/2018	125694/0	Modules 1, 2 and 3.
11/20/2018	125694/0.7 Response to CBER IR dated 10/18/2018	Reviewed responses to the PO-Q3 (tests performed in each DP release testing facilities).
11/20/2018	125694/0.9 Response to CBER PO IR dated 10/23/2018	Reviewed DP shipping OQ and PQ validation reports: RPT-877 and RPT-883
11/26/2018	125694/0.11 Response to CBER PO IR dated 10/23/2018	Reviewed filling and finishing PPQ report: PRO-429
1/17/2019	125694/0.21 Responses to the Filing Letter dated 11/29/2018.	Reviewed the responses to the DMPQ Questions 8 – 10. The Responses #9 (b) (4) processes) was inadequate, DMPQ sent another IR (dated 1/11/2019).
1/18/2019	125694/0.23 Responses to the DMPQ IR dated 1/07/2019	All responses to DMPQ questions of HVAC, flows and facilities were reviewed and accepted.
1/25/2019	125694/0.27 Responses to the DMPQ IR dated 1/11/2019	The Responses #3 (b) (4) was inadequate, which was discussed in the mid-cycle communication on 1/29/2019 and then during the PLI.
3/20/2019	125694/0.48 Responses to the FDA Form 483 (13-Observations, dated 2/8/2019)	The Responses #1, #2 and #11 were incomplete. CBER/DMPQ sent an Inspection-related IR (dated 3/27/2019).
3/22/2019	125694/0.50 Responses to the DMPQ IR dated 3/8/2019	The Response #1 regarding the (b) (4) freezers. CBER/DMPQ further communicated with the sponsor in an Inspection-related IR (dated 3/27/2019).
3/26/2019	125694/0.52 Responses to the DMPQ IR dated 3/14/2019	The Responses #1 and #3 were incomplete. CBER sent another IR (dated 3/27/2019).
4/9/2019	125694/0.56 Responses to Inspection-related IR (dated 3/27/2019)	The responses to CBER Inspection-related IR (b) (4) SOP-532).
4/11/2019	125694/0.59 Response to DMPQ IR (dated 3/27/2019)	The responses regarding issues of sterilization of (b) (4) and CCIT.
4/11/2019	125694/0.60 Responses to Late-Cycle Meeting (3/28/2019) identified issues	The response to the item d (major issue identified in the mid-cycle meeting) regarding reprocessing SOP-532 and summary report RPT-1320. Update Section 3.2.P.3.3.
4/24/2019	125694/0.67 Response to Inspection-related IR (dated 4/17/2019)	The responses to inspection-related IR regarding the specific conditions for (b) (4) of DP
5/7/2019	125694/0.75 Response to Inspection-related IR (dated 5/1/2019)	Reponses to inspection-related IR to update Section 3.2.P.3.
5/15/2019 and 5/16/2019	125694/0.81 and 125694/0.84 Responses to Inspection-related IR (dated 5/7/2019) and discussion points	The responses for including the Hold-time for the (b) (4) DP in the next (b) (4) study, providing disinfectant efficacy study reports, the description of

Date Received	Submission STN	Comments/Status
	for a teleconference (8May2019).	(b) (4) cleaning procedure.

## REVIEWER'S SUMMARY AND RECOMMENDATION

### Executive Summary

AveXis, Inc. (abbreviated as AveXis) submits an original Biological License Application (BLA, STN 125694/0, received by CBER on 10/03/2018) for a viral vector-based gene therapy product AVXS-101 (onasemnogene abeparvovec, ZOLGENSMA) for the treatment of pediatric patients with spinal muscular atrophy (SMA) Type 1. SMA Type 1 is a neurogenetic disorder caused by loss or mutations in the human survival motor neuron 1 gene (SMN1), resulted in reduced level of functional SMN protein. The drug product consists of AVXS-101 vector genome which (containing a recombinant human SMN gene (b) (4)) is encapsulated into AAV9 virions.

The drug product is formulated as sterile solution at a target concentration of  $2.0 \times 10^{13}$  vector genomes (vg)/mL, administered as a one-time-only intravenous (IV) infusion at a proposed dose of  $1.1 \times 10^{14}$  vg/kg, and indicated for the treatment of pediatric patients with SMA (b) (4).

The drug product is filled into 10 mL vials in either 5.5 mL volume (for 1 kg body weight) or 8.3 mL (for 1.5 kg body weight). The primary container closure system consists of a clear 10 mL (b) (4) vial, a gray 20-mm (b) (4) chlorobutyl elastomeric stoppers, and a 20-mm flip-off, aluminum seal with a colored (green) plastic button cap. Labels of individual vials are color-coded to differentiate two different fill volumes. A patient-specific commercial product kit (or Stock Keeping Units, SKU) consists of a configuration of up to (b) (4) 1.0 kg and 1.5 kg dose volumes of AVXS-101 DP based on patient's body weight.

The AVXS-101 Drug Substance (DS) and finished Drug Product (DP) are manufactured at AveXis' (b) (4) (FEI (b) (4)). The AVXS-101 (b) (4) DP release testing are performed at several different sites. FDA/CBER performed a 5-days pre-license inspection (PLI, conducted from (b) (4)) of the AVXS-101 (b) (4) manufacturing facility (FEI (b) (4)). The inspection of the AveXis (b) (4) manufacturing facility was concluded with thirteen observations and was classified as voluntary action indicated (VAI). The sponsor's responses to the 483 Observations were reviewed and accepted by inspectors.

FDA (Team Biologics and OTAT) performed a PLI (b) (4) of the AveXis (b) (4) Release Testing site (FEI: (b) (4)) because this site is a new Testing facility where (b) (4) critical potency tests are performed. CBER waived PLI of four DP release testing sites because these sites have been inspected by FDA Team Biologics or FDA/ORR with satisfactory GMP inspection outcomes (see an Inspection Waiver memo uploaded to EDR on 04Dec2018). The inspection of the AveXis (b) (4) Release Testing site was concluded with no observation (except discussion items) and was classified as

no action indicated (NAI).

CBER recommends two items may be followed up in a next FDA inspection: (b) (5), (b) (7)(E)

CBER understands that this recommendation may or may not be taken (based on risk and available resources), and is not requesting documentation to be submitted as evidence of completion.

## Recommendation

Approval of this Biological License Application, STN 125694/0, is recommended.

## Signature Block

Reviewer/Title/Affiliation	Concurrence	Signature and Date
W. Wang, CMC/Facility Reviewer, Lead Inspector, OCBQ/DMPQ/MRB1	Concur	
D. Trout, Team Lead, Inspector, OCBQ/DMPQ/MRB1	Concur	
C. Renshaw, Branch Chief, OCBQ/DMPQ/MRB1	Concur	
J. Eltermann, Division Director, OCBQ/DMPQ	Concur	

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## 3.2.S. DRUG SUBSTANCE

### 3.2.S.1. General Information


AVXS-101 is a (b) (4)

(b) (4)

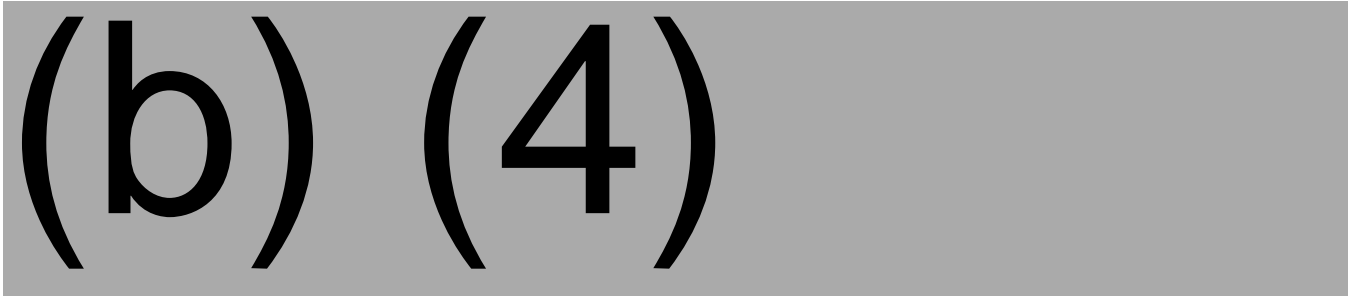
(b) (4)




(b) (4)



(b) (4)



(b) (4)


### 3.2.S.2. Manufacture

#### 3.2.S.2.1. Manufacturer(s)

The facility table (Table 1) is constructed based on following submitted information:

- Table 1 of Section 3.2.S.2.1. Manufacturer(s) in the original BLA submission, STN 125694/0.
- Table 3 of Section 1.11.1. Quality Information Amendment in an amendment, STN 125694/0.7.



- Table 1. Facilities and Responsibilities in Manufacture of AVXS-101 Drug Substances

Facility	Responsibilities
AveXis, Inc. (b) (4)	(b) (4)
AveXis, Inc. (b) (4)	(b) (4)
AveXis, Inc. (b) (4)	Drug Product Release Testing <ul style="list-style-type: none"> <li>(b) (4)</li> </ul> Stability testing <ul style="list-style-type: none"> <li>(b) (4)</li> </ul>
(b) (4)	(b) (4)

(b) (4)

**Reviewer's Comments:** The original BLA submission (STN 125694/0) did not contain certification confirming whether drug product release testing facilities are ready for inspection, which was listed as the item #8 in the filing letter (sent to AveXis on 11/29/2018). The sponsor confirmed (in Amendment STN 125694/0.21, received on 1/17/2019) that the drug product release testing facilities are ready for inspection. CBER performed a pre-license inspection (PLI, (b) (4), VAI) of the AVXS-101 (b) (4) manufacturing facility at (b) (4). FDA Team Biologics inspected (PLI, (b) (4), NAI) the AveXis DP release testing site at (b) (4).

During the PLI of the AveXis (b) (4) facility (FEI: (b) (4)), the sponsor informed the FDA inspection team members (including Wei Wang and Deborah Trout) that an (b) (4) (FEI: (b) (4)) was not yet equipped with refrigerators or freezers and was not commissioned for the storage of (b) (4) that need to be stored in refrigerator or freezers. CBER DMPQ sent an IR (dated 08Mar2019, Question #1) to request the sponsor to update the facility table with accurate usage information of the (b) (4) facility (FEI: (b) (4)). The sponsor updated the (b) (4) establishment information and corresponding contact information in FDA Form 356h (in STN 125694/0.50) and stated in Amendment, STN 125694/0.56 that AveXis agrees to only use freezers at the (b) (4) after they are qualified. The freezer qualifications will be included in the corresponding annual report.

### 3.2.S.2.2. Description of Manufacturing Process and Process Controls

(Documents reviewed: Section 2.3.S, Section 3.2.S.2.2, and Application Orientation Meeting Slides (dated 11/28/2018))

#### AVXS-101 (b) (4) Manufacturing Steps

(b) (4)

(b) (4)



(b) (4)

### 3.2.A.1. Facilities and Equipment

#### Facility

The AveXis facility (FEI: (b) (4) ) is located at (b) (4) . The manufacturing operations performed at the site include the commercial manufacture of the (b) (4) finished Drug Product, testing and storage of (b) (4) Drug Product. The GMP manufacturing suites consist of (b) (4) built cleanrooms and facilities, which are reviewed below and will be audited during a pre-license inspection (PLI) conducted during (b) (4) .

#### HVAC Systems

In Section 3.2.A.1. Facilities and Equipment (of STN 125694/0), the sponsor indicates that the Heating, Ventilation and Air Conditioning (HVAC) Systems are used to provide the AVXS-101 manufacturing facilities with clean air filtered through High Efficiency Particulate Air (HEPA) filters for containment and product protection, and that any open processing steps and connections are performed in ISO 5 classified spaces such as (b) (4) that are located inside a cGMP cleanroom.

(b) (4) Air Handling Units (AHU) are described to provide the air supply and return systems, and each AHU controls the environment within a cleanroom space associated with certain manufacturing step(s).

*Reviewer's Comments: The AveXis' HVAC systems and the (b) (4) were audited during PLI and were found acceptable to support the intended manufacturing activities.*

#### Cleanroom Areas, Flows and Diagrams

I reviewed diagrams (provided in Section 3.2.A.1. Facilities and Equipment – Diagrams, STN 125694/0) and requested the sponsor to address a few issues identified:

- Cleanroom Classifications (Diagrams RG0.01, RG0.01A and RG0.01B) – Information provided appears acceptable.
- Personnel flow (Diagrams RG0.02, RG0.02A and RG0.02B) – Information provided appears acceptable. Personnel flows through Personnel Airlocks (PAL) are also reviewed in Tables 2 to 9.
- Material Flow (RG0.03, RG0.03A and RG0.03B) – Information provided appears acceptable. Materials flows through Material Airlocks (MAL) are also reviewed in Tables 2 to 9.
- Air Pressurization Plans (RG0.07 A and RG0.07B) – Discrepancies of information regarding Air

Flow direction and Air Pressures in PALs (b) (4) next to the Fill Suite (b) (4) were noted. While the Air Pressurization Plan indicated air flow from the Fill Suite into PALs (b) (4) the air pressures indicated air flow from PALs into Fill Suite.

**Reviewer's Comments:** DMPQ requested the sponsor to clarify information discrepancies regarding air flow direction, and to clarify if (b) (4) is used by AHUs (Questions 1 and 2 of IR dated 7Jan2019). The Sponsor's responses (STN 125694/0.23, received on 18Jan2019) were reviewed (below in Section IR and Responses) and were accepted. The updated pressurization plan shows that air pressure cascade provides product protection in Fill suite:

Fill Suite (b) (4)  
 PAL-in (b) (4)  
 PAL-out (b) (4)

The sponsor also indicated that PALs (b) (4) cannot be opened at same time. The sponsor stated that (b) (4) is provided to the Production (b) (4) to allow (in future) simultaneous productions of (b) (4) different products (b) (4), and that (b) (4) manufacturing areas where only (b) (4) can be manufactured at a time.

- Emergency Exit – Information provided appears acceptable.
- Based on diagrams provided in Section 3.2.A.1. Facilities and Equipment – Diagrams of STN 125694/0, Cleanroom areas (b) (4) served by (b) (4) seems to be a standalone manufacturing unit and use (b) (4), compared with (b) (4)

**Reviewer's Comment:** DMPQ requested the sponsor to clarify if cleanroom areas served by (b) (4) are used for AVXS-101 (b) (4) DP commercial manufacturing activities (Question 3 of IR dated 7Jan2019). The Sponsor stated that (in Amendment STN 125694/0.23, received on 1/18/2019) that the cleanroom areas served by (b) (4) are only used for the manufacture of (b) (4).

- Product Flow – Information was found incomplete, bookmarks of several diagrams (including diagrams of Product Flow, Emergency Exit and Pressurization Plan) did not match the actual data sheet numbers.

**Reviewer's Comments:** DMPQ requested the sponsor to update Facility Diagrams (Question 4 of IR dated 7Jan2019). The Sponsor's responses (STN 125694/0.23, received on 1/18/2019) were reviewed (below in Section IR and Responses) and were accepted.

- Waste Flow – It seemed that (b) (4). It was unclear what waste materials are taken out through (b) (4)

**Reviewer's Comments:** During PLI I asked what kind of wastes are taken out of (b) (4) AveXis (Luke Lewis, Associate Director Manufacturing) explained to me that the only wastes in (b) (4) There is a (b) (4) No manufacturing waste is allowed to be taken out through (b) (4)



- (b) (4)

(b) (4)

(b) (4)

(b) (4)

### Major Equipment

The sponsor summarized major equipment for the manufacture of AVXS-101 (b) (4) Drug Product and indicated that major equipment listed in Table 10 is included in a Commissioning &



Qualification Plan which defines the strategy and deliverables of the commissioning and equipment qualification.

(b) (4)

(b) (4)

#### Water System

(b) (4)

**Reviewer's comment:** The usages of purchased (b) (4) was audited during the PLI (b) (4) and resulted in the 483 Observation # 7. The firm's responses were reviewed in 483 Responses Review Memo and accepted.

#### Facility Cleaning

In Section 3.2.A.1.1, the sponsor indicated that cleaning agents/disinfectants for cleaning of equipment and material (Table 11), or for cleaning of production suites (Table 12) have been qualified by performance of a disinfectant efficacy study.

Table 11. Agents/Disinfectants Used for Cleaning of Equipment and Material

(b) (4)

Table 12. Agents/Disinfectants Used for Cleaning of Production Suites

(b) (4)

**Reviewer's Comments:** The facility cleaning, including reports of disinfectant efficacy studies for cleaning agents, and procedures for equipment and cleanroom cleaning were further audited by an Investigator from Team Biologics during the PLI. No issues were found regarding facility cleaning. However, during the secondary review of the Establishment Inspection Report (EIR), it was questioned whether disinfectant effectiveness studies conditions (for example coupons vs. materials of equipment and facility surfaces) represent the actual facility cleaning (i.e. (b) (4) cleaning). DMPQ requested (IR dated 7May2019) the sponsor to provide information regarding the (b) (4) cleaning and disinfectant efficacy study results (see Section of Information Request and Responses). During a teleconference (on 21May2019), CBER informed the sponsor that a verification of (b) (5), (b) (7)(E)

### Cross Contamination Control

In section 3.2.A.1 of STN 125694/0, the sponsor stated that the AveXis (b) (4) Manufacturing facility is dedicated to the manufacture of AVXS-101, which eliminates the risk of cross-contamination.

### Environment Monitoring

In Section 3.2.A.1.1, the sponsor summarized (Table 13) its environmental monitoring (EM) program to perform routine monitoring of non-viable particulate (NVP), viable air particulates and viable surface particulates of each controlled environment manufacturing area under both static (At Rest) and dynamic (In-Operation) conditions.

**Reviewer's Comment:** Environment Monitoring schedules and data were further audited during PLI.

(b) (4)

(b) (4)

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

(b) (4)

### 3.2.S.2.3. Control of Materials

Control of materials (including Vender qualification and raw materials testing) were also audited during the PLI (b) (4)

I reviewed following material specification (SPEC) documents and defer to the Product Office to review other SPEC documents in Section 3.2.S.2.3. Control of Materials:

a. (b) (4)

b. (b) (4)

c. (b) (4)



- (b) (4)

(b) (4)

**Reviewer's Comments:** *The sponsor indicated (in Section 3.2.S.2.5. Process Validation and/or Evaluation of STN 125694/0) that any deviations if encountered during PPQ are mentioned following each table. DMPQ requested (Question 2 of IR dated 11Jan2019) the sponsor to provide any information of investigation of deviations (including the identification of potential root cause and any corrective and preventative action). The sponsor's response to this question (Amendment STN 125694/0.27, received on 25Jan2019) was reviewed below (in Section IR and Responses) and was accepted.*

(b) (4)

(b) (4)

(b) (4)

#### 3.2.S.4. Control of Drug Substance

(b) (4)





(b) (4)

(b) (4)

(b) (4)

### 3.2.P. DRUG PRODUCT

#### 3.2.P.3. Manufacture

##### 3.2.P.3.1. Manufacturer(s)

The facilities involved in the manufacture, testing, packaging, storage, and release of AVXS-101 DP are listed in Table 22. DMPQ waived the pre-license inspection of facilities where AVXS-101 DP release testing is performed (because these sites were recently inspected by FDA with acceptable inspection outcomes):

Table 22. Sites and Responsibilities in Manufacture of AVXS-101 Drug Product

Facility (Inspection or Inspection Waiver)	Responsibility
AveXis, Inc. (b) (4)	Raw Material Storage
	Excipient Storage
FDA FEI: (b) (4)	Drug Product
	Manufacture
	In-process testing
	Release testing
	Stability testing
PLI required (b) (4)	Stability sample storage
	Secondary labeling and packaging
	Final QA release
	Finished Drug Product storage
	Reference standard storage

Facility (Inspection or Inspection Waiver)	Responsibility
AveXis, Inc. (b) (4)    FDA FEI: (b) (4)	Raw Material Storage Excipient storage Finished Drug Product storage Reference standard storage  <b>Inspection not required</b>
AveXis, Inc. (b) (4)  FDA FEI: (b) (4)  <b>PLI required</b> (b) (4), Team <b>Biologics)</b>	Drug Product Release testing Stability testing
(b) (4)    	Drug Product Release testing Stability testing  <b>(Inspection Waived, last FDA Inspection in (b) (4), by CDER, VAI)</b>
(b) (4)    	Drug Product Release testing Stability testing  <b>(Inspection Waived, last FDA Inspection in (b) (4), by CDER, VAI)</b>
(b) (4)    	Drug Product Release testing Stability testing  <b>(Inspection Waived, last FDA Inspection in (b) (4), by ORA, VAI)</b>
(b) (4)    	Drug Product Release testing  <b>(Inspection Waived, last FDA Inspection in (b) (4), by ORA, VAI)</b>
(b) (4)    	Raw Material storage Finished Drug Product storage Reference Standard storage <b>(Inspection not required)</b>

### 3.2.P.3.2. Batch Formula

The AVXS-101 DP batch size is up to (b) (4), as the sponsor indicated in the Application Orientation Meeting on 30Nov2018). Due to the quantity of each input

AVXS-101 (b) (4) yield may vary, the amount of drug product (b) (4) to achieve a target concentration of  $2.0 \times 10^{13}$  vg/mL. AVXS-101 DP is filled into 10 mL (b) (4) vials with a nominal fill volume of either 5.5 mL (dosing for 1 kg body weight) or 8.3 mL (dosing for 1.5 kg body weight). The sponsor stated (in Section 3.2.A.3. of STN 125694/0) that there are no novel excipients used in the manufacture of AVXS-101 Drug Product.

The commercial batch formula and quantities of each component based on fill volume are provided in Table 23.

The AVXS-101 Drug Product manufacturing process does not include a specific formulation step, other components in the AVXS-101 Drug Product are included in the (b) (4) which is used to (b) (4) AVXS-101 (b) (4) in the (b) (4) the DP concentration in the Sterile Filtration (b) (4) step.

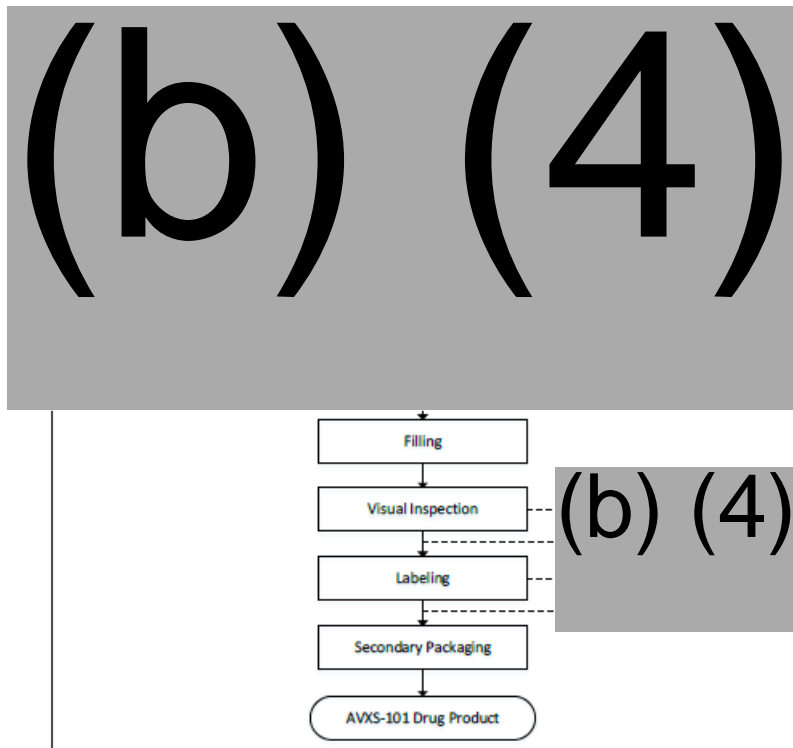
Table 23. AVXS-101 Drug Product Batch Formula

Component	Quality Standard	Quantity per mL	Quantity per 5.5 mL vial	Quantity per 8.3 mL vial
AVXS-101 Drug Substance	(b) (4)			
Tromethamine				
Magnesium Chloride				
Sodium Chloride				
Poloxamer 188				
(b) (4)				
(b) (4)				
(b) (4)				

### 3.2.P.3.3. Description of Manufacturing Process and Process Controls

The AVXS-101 Drug Product Manufacturing Process overview is depicted in Figure 8.

Figure 8. AVXS-101 Drug Product Manufacturing Process Overview (in original BLA submission)



The AVXS-101 Drug Product Manufacturing process consists of following 6 steps:

1. (b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

2. (b) (4)

[Redacted]



(b) (4)

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
3. **(b) (4) Filling.** The AVXS-101 drug product is filled aseptically (using an (b) (4) filling machine which has additional stations for stopper placement and vial capping) into ready-to-use, 10 mL (b) (4) vials. The vials are stoppered with (b) (4) ready-to-use 20 mm chlorobutyl rubber serum stoppers with (b) (4) coating, and then sealed with (b) (4), ready-to-use, aluminum seal with a colored plastic flip-off cap. AVXS-101 DP is filled into 10 mL vials with one of the two fill volumes: 5.5 mL for a 1.0 kg (body weight) dose and 8.3 mL for a 1.5 kg (body weight) dose.

The filling machine is located in a (b) (4) (see Figure 5 and Table 7 of this Review Memo) which provides an (b) (4) for the open operations, and the (b) (4) is in the (b) (4). The In-Process Manufacturing Controls for the (b) (4) are presented in Table 27:

**Reviewer's Comments:** In Master Batch Record MBR-(b) (4), AveXis describes the filling step in detail and indicates that following change parts (including (b) (4)

(b) (4) of the filler are sterilized. Cleaning and sanitization of (b) (4), and sterilization of change parts of filler were audited during PLI and found acceptable.

DMPQ requested (IR dated 14Mar2019) the sponsor to update the Section 3.2.A.1 (in STN

125694/0.59) regarding cleaning and sterilization of (b) (4) parts of the filler. Please see the Section IR and Responses for more information.

Table 27, Filling Process Parameters

Parameters	Parameters Categories	Range
Fill Weight	(b) (4)	(b) (4)
Processing Time		
Fill Weight		

Noted, the dose form-dependent Fill Weight range listed in Table 27 was for 5.5 mL and 8.3 mL fill volumes which were different from the AVXS-101 PPQ lots presented in Section 3.2.P.3.5 Process Validation and/or Evaluation of STN 125694/0 (reviewed below).

4. (b) (4) – **Visual Inspection.** The filled vials are transferred to the visual inspection area. The vials are 100% visually inspected by trained and qualified operators in a (b) (4). Each filled vial is inspected for defects, including compromised seals, incomplete closure, cracked vials, missing or incorrect container closure components, particles in solution, and foreign materials. The In-Process Manufacturing Controls for the (b) (4) are presented in Table 28:

Table 28. Visual Inspection Process Parameters

In-Process Controls	Action Limit
Material Accountability	(b) (4)
Visual Inspection AQL	
Container Closure Integrity (CCIT) by (b) (4)	

**Reviewer's Comments:** Noted, in Section 3.2.P.5.1. of STN 125694/0, the sponsor stated that "Container Closure Integrity per (b) (4) is only performed on stability; it is not part of the AVXS-101 Drug Product release specification". However, the sponsor confirms that 100% filled vials are subjected to CCIT by (b) (4) during the PLI (b) (4).

5. (b) (4) **Labeling.** The vials are manually labeled by operator in accordance with MBR instructions. Prior to the start of the batch, the label contents are inspected against approved label proofs and allocated to the batch. For vials stored at  $\leq -60^{\circ}\text{C}$  prior to labeling, the frozen state of the product is maintained through the labeling process.

The In-Process Manufacturing Controls for the (b) (4) are presented in Table 29:

Table 29. Labeling Process Parameters

In-Process Control	Action Limit
Label Accountability	(b) (4)
Labeling AQL	

**Reviewer's Comments:** CBER and the Sponsor had discussions (including a teleconference on 18Dec2018) regarding the storage of unlabeled vials under the condition of < -60°C and then labeling frozen vials. The sponsor indicated that this practice was due to the absence of the FDA approved labeling. The sponsor stated that after the FDA approval of labeling, all filled vials form (b) (4) lot will be labeled prior to be frozen at < -60°C, and that the identity test will be performed after all vials of each DP batch have been labeled.

FDA asked (pre-BLA, 8/23/2018) the firm to validate the labeling of frozen vials and to demonstrate that the labels remain adhere and readable after vial thaw. During the PLI (b) (4), the firm presented results of (b) (4) sets of labeling tests and informed the FDA inspector that the third labeling test was ongoing. DMPQ requested (IR dated 8Mar2019, Question #3) the sponsor to provide a summary report of labeling validation studies. The summary report of labeling validation RPT-1303 was received on 22Mar2019 (Amendment, STN 125694/0.50) and accepted.

(b) (4) – **Secondary Packaging.** Following disposition of the labeled AVXS-101 DP vials, the appropriate number of AVXS-101 DP vials (of 1.0 kg and 1.5 kg dose volumes) are packaged in a labeled carton (a patient specific kit) on (b) (4) during the packaging process. The commercial product kits, or Stock Keeping Units (SKU), will consist of a configuration of 1.0 kg and 1.5 kg dose volumes of AVXS-101 DP to allow for the appropriate dosing by weight of the patient.

The In-Process Control for the (b) (4) is the Accountability (Action Limit: 100%).

Table 30. Commercial Stock Keeping Units Configuration

SKU	(b) (4)
5.5 mL Vials	
8.3 mL Vials	
Nominal SKU Volume	

**Reviewer's Comments:** CBER and the sponsor discussed the secondary packaging/commercial product kit via a teleconference (on 18Dec2018) regarding whether the proposed vial labeling (i.e. a label of each filled vial has a color-coded dot specific for the dose form in vial) is sufficient to differentiate the weight-dependent dosing. The firm stated that, in addition to using color-coded dots on the vial labeling, filled vials can be differentiated by fill size (i.e. 5.5 mL vs. 8.3 mL). The sponsor presented information of packaging workflow for a patient-specific commercial product kit, Raw Material and Intermediate Lot Traceability during manufacturing, and Finished Product Kit Lot Traceability during distribution). I defer to the APLB reviewers to further evaluate



*GMP compliances of the proposed vial labeling and inserts for secondary packaging.*

*During the Mid-Cycle Communication Meeting, the firm proposed to extend the patients' weight range from the original (b) (4). DMPQ requested (IR dated 8Mar2019, Question #2) the firm to provide information on secondary packaging configurations and a shipping validation summary report for Drug Product dosed for patients' weight range between (b) (4) – 13.5 kg. The shipping validation summary report (RPT-921) was received on 22Mar2019 (Amendment STN 125694/0.50) and was accepted. No further question was asked.*

### 3.2.P.3.4. Control of Critical Steps and Intermediates

The In-Process Manufacturing Controls for the AVXS-101 Drug Product manufacturing are as described above in Section 3.2.P.3.3. I defer to the Product Office reviewers to further evaluate the adequacies of action limits set for in-process controls.

### 3.2.P.3.5. Process Validation

#### Process Performance Qualification

The sponsor stated that four consecutive Process Performance Qualification (PPQ) runs were completed for the AVXS-101 DP manufacturing process. The PPQ lots information is summarized in Table 31:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



(b) (4)

### Shipping Validation

In the original BLA submission, STN 125694/0, the sponsor indicated that shipping validation studies for the AVXS-101 Drug Product are ongoing, which consists of three studies: design and development, container operational qualification studies, and product performance qualification studies. The sponsor did not provide shipping validation information (e.g. Shipping Validation Master Plan, Shipping SOPs and any shipping validation data) in STN 125694/0.

***Reviewer's Comments:** The lack of Shipping Validation information was listed as an information deficiency (#10 of the filing letter issued by CBER on 11/29/2018). The sponsor provided following shipping validation reports in Section 3.2.P.3 of Amendment STN 125494/0.9 (received by CBER on 20Nov2018) and in Section 1.11.4 of Amendment STN 125694/0.21 (received by CBER on 1/17/2019):*

- **RPT-877 – AVXS-101 Shipping Validation Operational Qualification (OQ) Summary Report** – summarized both the (b) (4) per PLAN-178 and the Distribution OQ per PRO-550.

(b) (4) AVXS-101 DP is filled into 10 mL (b) (4) vials to a nominal volume of either 5.5 or 8.3 mL and frozen at  $\leq -60^{\circ}\text{C}$ . (b) (4) vials (varies based on patient dosing requirements) are loaded into a carton that contains a (b) (4) vial insert for distribution to the site of care.

For shipments of the AVXS-101 DP from the AveXis (b) (4) site to the domestic sites, the (b) (4) is utilized with packed (b) (4) to maintain shipment temperatures  $\leq -60^{\circ}\text{C}$  until receipt at the site of care.

(b) (4) used an independent, (b) (4), 3<sup>rd</sup> party testing facility to perform (b) (4) testing on the standard (b) (4) when exposed to a (b) (4) and (b) (4) test profile.

It was stated that the (b) (4) maintained internal product payload temperatures below  $-60^{\circ}\text{C}$  for a minimum of (b) (4) consecutive hours using a minimum of (b) (4) and when exposed to a (b) (4) and (b) (4) test profile, and that the (b) (4) monitoring was capable of continuous monitoring of parameters, and the data was reliable, accessible, accurate, and retrievable throughout shipping process.

But, when the (b) (4) packaging temperature profile being set for up to (b) (4), the hold time was (b) (4) hours and (b) (4) minutes (while maintained temperature at  $\leq -60^{\circ}\text{C}$ ), which failed to meet the (b) (4) hours acceptance criteria without (b) (4) capabilities. Thus, (b) (4) procedures were incorporated into PRO-552 AVXS-101 Shipping Validation Performance Qualification.

Distribution OQ For the Distribution OQ, the AVXS-101 Drug Product Placebo was packaged into the (b) (4) per PRO-550 (b) (4) vials per carton each configuration). Shipping of

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

(b) (4)

(b) (5) DPP, (b) (5) ACP, (b) (5) ADP

(b) (4)

[illegible]

### Computerized System

In Section 3.2.A.1 of STN 125694/0, the sponsor summarized following computerized systems utilized for control of manufacturing processes of AVXS-101 (b) (4) drug product:

- The Supervisory Control and Data Acquisition (SCADA) system displays and monitors critical facility and process data. The system provides the platform to configure alarms for critical environmental controls and to capture an alarm response with user authentication.
- The Building Management System (BMS) provides a plant wide overview and data collection (e.g., from Air Handling Units, (b) (4), etc.) of the Building Management System equipment.
- The GMP Server & Infrastructure is used to provide a secure network and virtual machine

environment, to support the plant SCADA system and building management system (BMS) applications.

- (b) (4) is an Enterprise Resource Planning (ERP) inventory control software used to track inventory and status of materials throughout the facility and lifecycle of the material.

*Note, the validation and qualification of computerized systems was also audited during the PLI by FDA Investigator (Team Biologics). No objectionable issues were identified.*

### 3.2.P.5. Control of Drug Product

#### 3.2.P.5.1. Specifications and 3.2.P.5.2. Analytical Procedures

Per SOPP 8404.4, I reviewed microbiological assay procedures for sterility and endotoxin. I defer to the reviewers from the Product Office and DBSQC to further review the testing method validation and qualification. Validation of QC Microbiological Testing procedures will be audited by the Product Reviewer.

- Endotoxin is tested per (b) (4) (AveXis SOP-121) with acceptance criterion of (b) (4). AveXis utilizes the (b) (4), developed by (b) (4), licensed in (b) (4) and accepted by (b) (4) for testing Endotoxin in raw materials, in-process samples and final products.
- Sterility is tested per (b) (4) (AveXis SOP-337) with acceptance criterion of “No Growth”. The analysis of sterility by (b) (4) for the AVXS-101 Drug Product release testing is performed by the AveXis approved contractor, (b) (4).

The container closure integrity testing (CCIT) by (b) (4) method is described in a validation report RPT-447 in Section 3.2.P.5.3 of STN 125694/0.

#### 3.2.P.5.4. Batch Analyses

The sponsor summarized different versions of acceptance criteria for the release of the AVXS-101 Drug Product. Noted, the specification Sterility (Table 33) has remained unchanged during the drug product development, whereas the specification for Endotoxin was changed from (b) (4) (earlier versions) to (b) (4) (commercial drug product specification).

The sponsor footnoted (Table 2 of Section 3.2.P.5.4 of 125694/0, page 7/13) that the previous specifications were not used to release any lots. But, the PPQ lots data (Table 3 of Section 3.2.P.5.4 of STN 125694/0, pages 8/13 – 9/13) showed that the previous specifications (e.g. pH, and Endotoxin) were used to release PPQ lots.

**Reviewer's Comment:** *Noted, in Table 3 of Section 3.2.P.5.4 of STN 125694/0 (page 9/13) it was shown that the named impurity (b) (4) was detected only in the (b) (4) PPQ lots. However, in Table 7 of Section 3.2.P.3.5 of STN 125694/0 (page 13/27) it was shown that the (b) (4) was detected in the (b) (4) PPQ Lot (b) (4) and the (b) (4) was detected in the (b) (4) PPQ Lot (b) (4).*

*It was unclear why the impurity data for a same PPQ lot (i.e. Lot (b) (4)) were reported differently in two sections of the original BLA submission. DMPQ requested (IR dated 8Mar2019, Question 5). The sponsor stated in Amendment, STN 125694/0.50 (received on 22Mar2019) that results for (b) (4) for Lot (b) (4) in the process validation section 3.2.P.3.5 represent a transcription error in the associated process validation report. The sponsor revised Section 3.2.P.3.5 with correct values for (b) (4) of Lot (b) (4) in the Amendment, STN 125694/0.50. No further question was asked.*

Table 33. Summary of Process B AVXS-101 Drug Product Specification Changes

Attribute	Specification Version 5.0 <sup>a</sup>	Specification Version 6.0, 7.0 and 8.0	Specification Version 9.0	Specification Version 10.0	Proposed Commercial Specification
Appearance	Clear to slightly opaque, colorless to faint white solution, free of visible particulates	No Change	No Change	No Change	No Change
pH	(b) (4)	No Change	No Change	No Change	(b) (4)
(b) (4)	(b) (4)	No Change	No Change	No Change	No Change
(b) (4)	(b) (4)	No Change	(b) (4)	No Change	No Change
(b) (4)	Report Result	No Change	No Change	No Change	(b) (4)
Endotoxin	(b) (4)	No Change	No Change	No Change	(b) (4)
Sterility	No Growth	No Change	No Change	No Change	No Change

<sup>a</sup>Previous specifications seemed to be used to release PPQ lots.

The sponsor provided release data for the (b) (4) PPQ lots and showed that Sterility and Endotoxin testing results of all (b) (4) PPQ lots met specifications: Sterility results were “No growth” for all (b) (4) PPQ lots, and Endotoxin results were (b) (4) for all (b) (4) PPQ lots. Noted, PPQ lots were released per previous specifications, and the (b) (4) lots (b) (4) were indicated for clinical use (Table 1 of Section 3.2.P.5.4 of STN 125694/0, page 4/13).

### 3.2.P.7. Container Closure System

#### Primary Packaging – Drug Product

For both Dose Forms (i.e. Fill Volume 5.5 mL for 1 kg-dose and Fill Volume 8.3 mL for 1.5 kg-dose) the

container closure system components are summarized in Table 34:

**Table 34. Summary of AVXS-101 Drug Product Primary Packaging Components**

Component	Manufacturer and Address	Description (Manufacturer Product Number)	Function	DMF
Vial	(b) (4)	10 mL (b) (4), cyclic olefin polymer, vial. <ul style="list-style-type: none"> <li>Sterile, Ready to Use (b) (4)</li> </ul>	Container	BB-MF (b) (4)
Stopper	(b) (4)	20 mm (b) (4), chlorobutyl elastomeric stopper, (b) (4). <ul style="list-style-type: none"> <li>Sterile, Ready to Use (b) (4)</li> </ul>	Closure	BB-MF (b) (4) Stopper) (b) (4)
Aluminum Seal with Plastic Button Cap	(b) (4)	20 mm flip-off, aluminum seal with a light green button and clear lacquer. <ul style="list-style-type: none"> <li>Sterile, Ready to Use (b) (4)</li> </ul>	Closure	N/A

**Vials:** The 10 mL (b) (4) clear plastic vials are manufactured by (b) (4). The (b) (4) vials are tested by the vendor to meet the requirements of following tests and Quality Control testing results are confirmed on the Quality Certificate:

- Plastic Packaging Testing per (b) (4)
- Bacterial Endotoxin Testing per (b) (4)
- Biological Reactivity Tests per (b) (4)

Prior to using, AveXis quality control (QC) conducts incoming testing of the vial for appearance, dimensions, and confirmation of test results from the supplier (Certificate of Analysis/Quality Certificate). Upon completion of these quality controls, AveXis quality assurance (QA) releases the vials for use.

**Stoppers:** The (b) (4) 20 mm, (b) (4) stoppers are manufactured by (b) (4). The stoppers are (b) (4), sterilized and provided in a ready to



use format. The stoppers are tested by the vendor to meet the requirements of Elastomeric Closures per (b) (4).

Prior to using, AveXis quality control (QC) conducts incoming testing of the stoppers for appearance, dimensions, and confirmation of test results from the supplier (Certificate of Analysis/Quality Certificate). Upon completion of these quality controls, AveXis quality assurance (QA) releases the stoppers for use.

**Seals:** The aluminum 20 mm flip-off seal with a colored plastic button cap are produced by (b) (4). The (b) (4) seals consist of an aluminum shell and a plastic (polypropylene) button that are tamper-evident. The seals are manufactured with (b) (4) to assure that the seals meet tight dimensional standards. The seals are cleaned, sterilized, certified and provided in a ready to use format.

Prior to using, AveXis quality control (QC) conducts incoming testing of the seals for appearance, dimensions, and confirmation of test results from the supplier (Certificate of Analysis/Quality Certificate). Upon completion of these quality controls, AveXis quality assurance (QA) releases the seals for use.

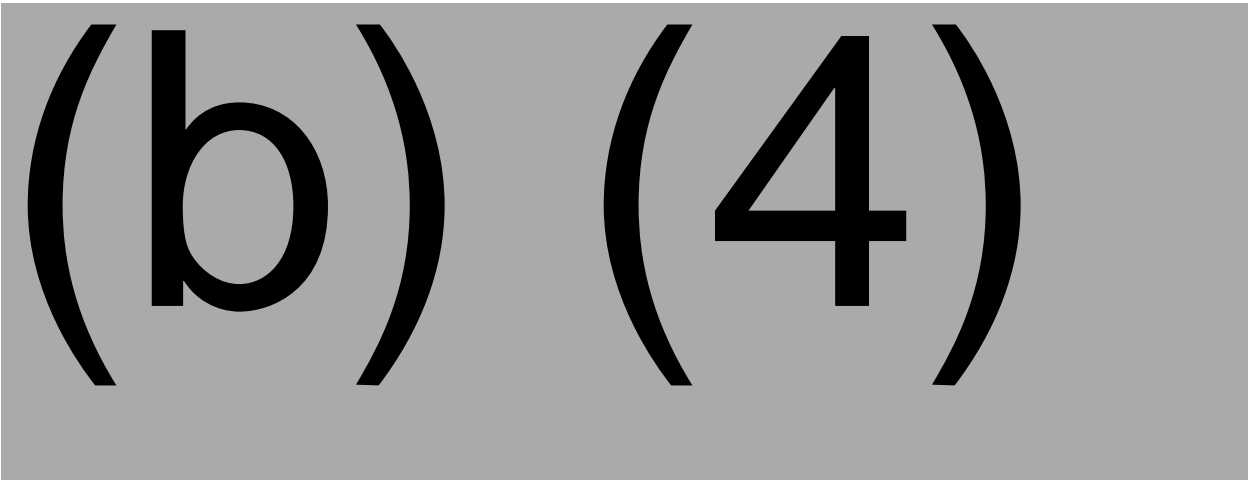
The sponsor described dimensions of the primary packaging components and provided technical schematic for 10 mL (b) (4) vial, 20 mm stopper and 20 mm flip-off seal.

***Reviewer's Comments:*** No review issues were identified. The testing of sterility and Endotoxin of the ready-to-use sterile container closure system components were audited during the PLI.

### 3.2.P.8. Stability

The firm summarized in Section 3.2.P.8.1 Stability Summary and Conclusions (of STN 125694/0) that four DP lots manufactured by the commercial manufacturing process (i.e. Process B) were stored in small-scale representative container closure system for stability studies (Table 35). The long-term Stability Protocol is summarized in Table 36.

Table 35. AVXS-101 Drug Product Stability Studies



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

(b) (4)

(b) (4)

*As show in Table 35, the firm provided limited stability data in the original BLA submission (STN 125694/0). I defer to the Product Office reviewers to evaluate the adequacy of stability data in order to support the proposed shelf-life for AVXS-101.*

## INFORMATION REQUESTS (IR) AND RESPONSES

IR dated 7Jan2019

The following IR items were sent to AveXis on 7Jan2019, and the Sponsor's responses were received on 18Jan2019 (Amendment, STN 125694/0.23):

1. Air Flow – In the Air Pressurization Plan (RG0.07A), Air Flow direction was illustrated from the (b) (4). However, the air pressures indicate that air flow direction is from PALs (b) (4) into the (b) (4). Air Flow from PAL ((b) (4)) into the (b) (4) appears to be an issue. Please clarify this information discrepancy. Please clarify if doors of the two PALs (b) (4) may be open at a (b) (4).

Sponsor's Response: The sponsor stated that Drawings RG0.07 and RG0.07A have been corrected and included followings:

- Fill Suite, (b) (4)
- PAL (b) (4)
- PAL (b) (4)

The sponsor indicated that PALs (b) (4) opened at (b) (4)

Reviewer's Comment: *The sponsor's response was accepted*

2. Please clarify if (b) (4) is used. If not, please provide justifications.

Sponsor's Response: The original facility design requirement was to provide a facility where two different products could be manufactured at the same time or simultaneously in the (b) (4) manufacturing space in the PODs. With production (b) (4) to meet this requirement, 100% (b) (4) was required in the (b) (4) areas of the PODs (b) (4). For (b) (4), the facility is not designed for two different products at the same time, therefore the air

(b) (4)

*Reviewer's Comment: The firm's response appeared acceptable.*

3. Based on diagrams provided in Section 3.2.A.1. Facilities and Equipment – Diagrams of STN 125694/0, Cleanroom areas (b) (4)

Please clarify if cleanroom areas served (b) (4) are used for AVXS-101 (b) (4) DP commercial manufacturing activities.

Sponsor's Response: The cleanroom areas served by (b) (4) is used for (b) (4) manufacturing activities only.

*Reviewer's Comment: It is not clear which (b) (4)*

4. In Section 3.2.A.1. Facilities and Equipment – Diagrams of STN 125694/0, Bookmarks RG0.05, RG0.05A, RG0.05B, RG0.07 and RG0.07A did not match the actual Sheet Numbers of these diagrams. Product Flow information was incomplete. Please update the Section with correct and complete flow diagrams.

Sponsor's Response: In the response to the Question 1 of IR dated 7Jan2019, the sponsor indicated that the drawings in the original BLA submission (STN 125694/0) were Project drawings and have been migrated to the new AveXis drawing management system (DMS) with new drawing numbers. The sponsor updated Section 3.2.A.1 Facilities and Equipment - Diagrams.

*Reviewer's Comment: The sponsor's response was accepted.*

5. The AHU serving the PAL (b) (4) was not indicated in Table 4 "Cleanrooms, Environmental Classifications, and AHUs" of section 3.2.A.1 Facilities and Equipment of STN 125694/0.

Sponsor's Response: The sponsor indicated that PAL (b) (4) is served by (b) (4), and updated Table 4 of Section 3.2.A.1.

*Reviewer's Comment: The sponsor's response was accepted.*

6. Please indicate the air pressure for the room number (b) (4) – PAL).

Sponsor's Response: the sponsor indicated that the air pressure for room number (b) (4) is controlled at a pressure of (b) (4)

Reviewer's Comment: *The sponsor's response was accepted.*

IR dated 11Jan2019

The following IR items were sent to AveXis on 11Jan2019, and the Sponsor's responses were received on 25Jan2019 (Amendment, STN 125694/0.27):

1. Validation of HVAC – Please provide a validation summary for the HVAC system with the following information:
  - A narrative description of the validation process (or protocol), including the acceptance criteria.
  - Certification that IQ, OQ and certification of filters has been completed.
  - Length of the validation period.
  - A validation data summary (include Performance Qualification data accumulated during actual processing).
  - Explanations of any excursions or failures, including deviation reports and summary of investigation results.

Sponsor's Response: AveXis performed Installation Verification (IV), Operational Verification (OV) and Environmental Monitoring Performance Qualification (EMPQ). The IV consists of verification of SOP(s), Drawings(s), Instrument Calibrations, HEPA filter certificates, equipment/component verification, Spare parts, Software, Code Review, and Alarm configuration. OV consists of Alarm verification including delays and setpoints, HVAC sequence of operations testing, VFD fault testing and fire system interlock testing. EMPQ consists of sampling sites throughout the manufacturing facility as identified by Quality Control Environmental Monitoring team based on (b) (4) and ISO-14644 requirements. Samples sites were selected for testing for non-viable air particulates, viable air, passive air and viable surface.

Acceptance criteria for IV/OV included: HEPAs required to be (b) (4)

Acceptance criteria for EMPQ is listed in each report (RPT) below:

- (b) (4)

Length of the validation period – EMPQ was performed per the following manufacturing areas:

- (PODs): (b) (4) (RPT-333 v3.0, Appendix 2: Sampling Dates)
- (b) (4) (RPT-849 v2.0, Appendix 3: Sampling Dates)
- (b) (4) (RPT-908 v1.0, Appendix

#### 4: Sampling Dates)

A list of validation report (include Performance Qualification data accumulated during actual processing).

- Manufacturing Area (PODs): RPT-333 v3.0, Section 6
- Manufacturing Area (b) (4) RPT-849 v2.0, Section 4
- Manufacturing Area (b) (4) RPT-908 v1.0, Section 4

Explanations of any excursions or failures, including deviation reports and summary of investigation results.

- Excursions or failures, during the EMPQ execution are documented in the following:
- Manufacturing Area (PODs): RPT-333 v3.0, Section 6.6
- Manufacturing Area (b) (4) RPT-849 v2.0, Section 4.2,
- Table 8
- Manufacturing Area (b) (4) RPT-908 v1.0, Section 4.2, Table 9.

*Reviewer's Comment: Some of above listed validation reports (including Environment Monitoring Performance Qualification Report RPT-333 and HEPA filter recertifications) were further audited during PLI and were accepted.*

2. Deviations and Investigation – You indicated (in Section 3.2.S.2.5. Process Validation and/or Evaluation of STN 125694/0) that any deviations if encountered during Process Performance Qualification (PPQ) are mentioned following each table. You indicated that the PPQ lot (b) (4) was discarded shortly (b) (4) due to contamination. The information of deviation investigation was not provided. Please provide summary of investigation results including the identification of possible route of cause and any corrective and preventative actions.

Sponsor's Response: The (b) (4) contamination of PPQ lot (b) (4) was investigated through (b) (4). The investigation confirmed that the (b) (4)

(b) (4)

(b) (4)



17Apr2019).

IR dated 8Mar2019

The following IR items were sent to AveXis on 8Mar2019, and the Sponsor's responses were received on 22Mar2019 (Amendment, STN 125694/0.50):

1. During the Pre-license Inspection (PLI) of your (b) (4) manufacturing facility (FEI: (b) (4)), you informed the FDA inspectors that the (b) (4) (FEI: (b) (4)) had not been equipped with refrigerators or freezers for the storage of (b) (4), and it was not currently being used for storage of materials or product. Please update the facility table in your application with the accurate usage information of the (b) (4) (FEI: (b) (4)).

Sponsor's Response: The (b) (4) establishment information and corresponding contact information have been updated in the application form (356h) and is included in this submission.

Reviewer's Comments: DMPQ sent the following (as the Item#1 of an Inspection Related IR dated 27Mar2019) to the sponsor "Although you have updated the Form 356h (in Amendment, STN 125694/0.50) to indicate the (b) (4) (FEI# (b) (4)) may also be used for the storage of materials (including Finished Drug Product and Reference Standard), you cannot use freezers in this site until you have completed equipment qualification for freezers used for storage. The freezer qualification will not be reviewed with your BLA but can be reported in your Annual Report post approval upon the completion of the freezer qualification". The sponsor stated in Amendment, STN 125694/0.56 (received 09Apr2019) that AveXis agrees to use freezers at the (b) (4) only after they are qualified. The freezer qualifications will be included in the corresponding annual report.

2. You recently proposed to revise the patients' weight range from (b) (4) – 13.5) kg. Please provide information on secondary packaging configurations and a shipping validation summary report for Drug Product dosed for patients' weight range between (b) (4) – 13.5 kg.

Sponsor's Response: The patient weights range up to 13.5 kg requires up to 9 vials to be included in the secondary packaging with combinations of the proposed vial presentations. The same proposed carton is to be utilized for all secondary packaging configurations with eight different vial platforms to provide doses containing 2 to 9 vials in a single carton.

A shipping validation was performed to evaluate these secondary packaging configurations with the intended shipping container and distribution lanes. The shipping validation report RPT-921 provided following information:

#### **AVXS-101 Drug Product Secondary Packaging Configuration**

AVXS-101 DP is filled into 10 mL clear plastic vials to a nominal volume of either 5.5 (dose for 1 kg of body weight) or 8.3 mL (dose for 1.5 kg of body weight) and frozen at ≤ -60°C. Labeled vials of AVXS-101 DP are subsequently packaged with a packaging insert and alcohol wipes into cardboard cartons containing 2 to 9 vials. The cardboard cartons are a two-piece full telescoping



rigid set box. There are eight vial inserts that hold 2 to 9 vials. The load configuration is dependent on the Stock Keeping Unit (SKU) defined.

### Shipping Container

A cardboard carton containing DP vials is loaded into a pre-conditioned shipping container. The shipping container is packed with (b) (4) to maintain shipment temperatures  $\leq -60^{\circ}\text{C}$  as following:

Description	Model	Payload	Temperature Management	Temperature
(b) (4)				$\leq -60^{\circ}\text{C}$

(b) (4)

### Shipping Lanes

The shipping container is distributed along shipping lanes pre-determined by the courier service to the registered Site of Care (SOC) or Novartis facility. Based on the pre-determined shipping lanes, the estimated worst-case lane is summarized below.

The Worst-case Shipping Lane Estimates:

Description	Origin	Origin Pickup Time	SP Delivery-Pickup Time	SOC Delivery Time <sup>1</sup>	Destination	Est. Flights	Est. Transit Time
United States	AveXis (b) (4)	(b) (4)					

(b) (4)

**Reviewer's Comments:** The sponsor stated that "United States distribution may route the AVXS-101 DP directly to the SOC or through a Specialty Pharmacy (SP) for additional labeling". The sponsor has not previously mentioned any additional labeling by a SP. I defer to the Product Office Reviewer to further evaluate the adequacy of activities performed by SP.

### Thermal Operational Qualification (OQ)

Thermal quality studies were conducted to ensure the (b) (4) Shipping Container can maintain the product load at  $\leq -60^{\circ}\text{C}$  throughout the anticipated transit.

The sponsor summarized the Acceptance Criteria and Results of a Thermal Operational

Qualification – Average Thermal Profile that was previously provided in the BLA submission and was reviewed/accepted (RPT-877, AVXS-101 Shipping Validation Operational Qualification Summary Report).

#### Distribution Operational Qualification

Distribution simulations were conducted to ensure the (b) (4) Shipping Container is able to withstand handling, vibration and environmental conditions while protecting the product from damage during transit. The Distribution Operational Qualification Test Conditions and the Acceptance Criteria and Results for Distribution Operational Qualification (b) (4) Vial Configuration were also provided in the original BLA submission and were reviewed/accepted in RPT-877, AVXS-101 Shipping Validation Operational Qualification Summary Report.

Change Control Record CCR-365, Introduction of 9 Vial Carton Insert for Secondary Packaging, introduced a maximum configuration consisting of up to 9 vials utilizing the same carton previously used in distribution simulation testing. The distribution simulation was repeat with the following payload and shipping configuration for testing:

Test Condition	AVXS-101 DP Configuration	(b) (4)	Shipping Container Packaging
Maximum Load	(b) (4) holding 9 vials	(b) (4)	(b) (4)

The sponsor provided data indication all distribution qualification testing results met the preset acceptance criteria (including Post Testing Visual Inspection - The package was opened for (b) (4) minutes and nothing unusual were observed during visual inspections, and Payload Temperature Monitoring - The payload temperature remained  $\leq -60^{\circ}\text{C}$ ).

#### Performance Qualification

The AVXS-101 DP Shipping Validation Performance Qualification (PQ) (RPT-883 for up to (b) (4) per carton) was conducted to confirm the (b) (4) Shipping Container has no impact to the AVXS-101 DP through simulated worst-case supply lanes.

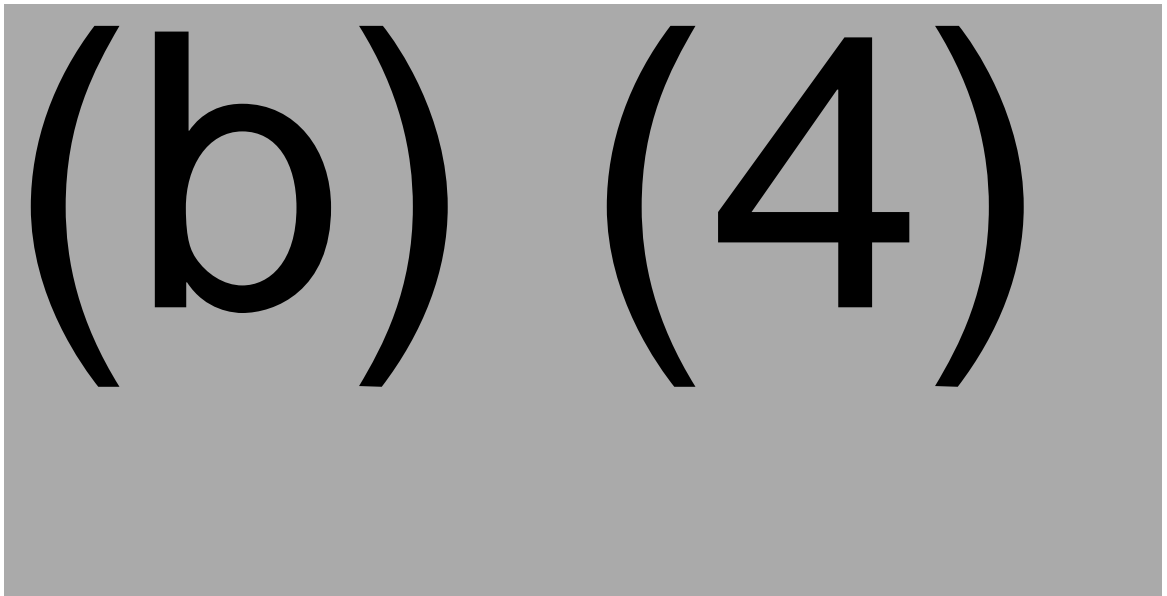



The PQ was previously performed with the (b) (4) Shipping Container to evaluate a (b) (4) vial payload in duplicate and a 2-vial payload. Results of the performance testing showed no impact to previous configurations in the commercial secondary packaging and no difference between 2 and (b) (4) vial payloads under simulated shipping lanes. The additional (b) (4) through 9 vial platforms will utilize the same carton under the same shipping conditions previously validated; therefore, additional vials per carton is not expected to impact the product quality and is supported by the results of the distribution simulation. No additional PQ activities were therefore performed.

**Reviewer's Comments:** *Noted, in RPT-877 and RPT-883, the sponsor indicated that the carrier will replenish the shipper with (b) (4) every (b) (4). The sponsor's shipping validation data in the summary report RPT-921 was accepted.*

- Please provide a summary report of label validation studies to demonstrate that labels applied to frozen vials remain adhere and readable after thaw.

Sponsor's Response: The sponsor provided a report RPT-1303 to summarize interim data from an ongoing labeling validation study. This labeling validation study started on 16Jan2019.

(b) (4)



*Reviewer's Comments:* *The interim data from an ongoing labeling validation study provided in this report RPT-1303 was accepted.*

4. During the Pre-license Inspection (PLI) of your (b) (4) manufacturing facility (FEI: (b) (4), you informed the FDA inspectors that, due to air pressure and air flow issues, you (b) (4)

(b) (4) Please confirm.

Sponsor's Response: The sponsor confirmed that the (b) (4) per NCR-1165 and work order 5970.

Reviewer's Comments: *The sponsor's response was accepted.*

5. We noted the following information discrepancy in your BLA submission (STN 125694/0) regarding the impurities in the (b) (4) PPQ lots (b) (4). Please provide a brief explanation of why the same set of data were reported differently in two sections of BLA submission.

In Table 3 of Section 3.2.P.5.4 of STN 125694/0 (page 9/13) it was shown that the (b) (4) was detected only in the (b) (4) PPQ lots (Lot (b) (4)).

In Table 7 of Section 3.2.P.3.5 of STN 125694/0 (page 13/27) it was shown that the (b) (4) was detected in the (b) (4) PPQ Lot (b) (4) and the (b) (4) was detected in the (b) (4) PPQ Lot (b) (4).

Sponsor's Response: The results for (b) (4) for Lot (b) (4) in the process validation section 3.2.P.3.5 represent a transcription error in the associated process validation report.

The results in section 3.2.P.5.4 for Lot (b) (4) are confirmed to be correct for both (b) (4) (not detected or ND) and for (b) (4). Section 3.2.P.3.5 has been revised to correct values for (b) (4) Lot (b) (4) and is included in this submission.

Reviewer's Comments: *The sponsor's response was accepted.*

## IR dated 14Mar2019

The following IR items were sent to AveXis on 14Mar2019, and the Sponsor's responses were received on 26Mar2019 (Amendment, STN 125694/0.52):

1. During the pre-license inspection (PLI), we noted that some parts of the filler are (b) (4). Please update the BLA submission Section 3.2.A.1 with information of cleaning and sterilization of (b) (4) parts.

Sponsor's Response: The filler parts that are (b) (4) are not direct product contact. All direct product contact parts are single use. During manufacturing, some (b) (4) parts do come in contact with the stoppers and caps. These parts are cleaned at the vendor with a (b) (4) and are sterilized using a validated (b) (4) at our qualified vendor.

Reviewer's Comments: *The Sponsor's response was incomplete. DMPQ requested the sponsor to provide the requested information (see IR dated 27Mar2019).*

2. In Section 3.2.S.2.2 of STN 125694/0 you stated that the (b) (4)

(b) (4) is discarded after each batch (i.e., the (b) (4) (b) (4) During the PLI we noted that a (b) (4) was mentioned in the (b) (4) (b) (4). It was not clear if the resin is discarded but the (b) (4) is (b) (4). Please clarify.

Sponsor's Response: The (b) (4)

*Reviewer's Comments: The sponsor's response was accepted.*

3. Please address the suitability of your Container Closure Integrity Test method (i.e. CCIT by (b) (4) ) to detect the potential compromised container closure integrity due to loss of elastic properties of the CL Butyl stopper (material number (b) (4) ) during the long term (up to (b) (4) storage at  $\leq -60^{\circ}\text{C}$ . Information provided should address the potential regaining of elastomeric properties of the stopper and the re-sealing of the container closure system once thawed.

Sponsor's Response: The Container Closure Integrity Test, utilizing a (b) (4) method, was validated for the AVXS-101 Drug Product presentation at ambient temperature conditions. The results of the validation demonstrate that the method is capable of detecting (b) (4) (b) (4) s. Details of the method validation are provided in 3.2.P.2.4. This test method is utilized to evaluate CCIT at discrete timepoints throughout the AVXS-101 Drug Product stability program after thawing the AVXS-101 Drug Product held in long term storage.

For purposes of evaluating potential loss of elastomeric properties of the stopper at storage conditions  $\leq -60^{\circ}\text{C}$ , a Container Closure Integrity Test, utilizing a (b) (4) method, was validated for the AVXS-101 Drug Product presentation held at (b) (4) The results of the validation demonstrate that the method is capable of detecting (b) (4) (b) (4) . This test method was utilized in evaluating the container closure integrity of the AVXS-101 Drug Product after being challenged under (b) (4) . The results of the (b) (4) study indicated no loss of container closure integrity after (b) (4) (b) (4)

*Reviewer's Comments: The Sponsor's response was incomplete. DMPQ requested the sponsor to provide the requested information (see IR Item#2 dated 27Mar2019).*

#### IR dated 27Mar2019

The following IR items were sent to AveXis on 27Mar2019, and the Sponsor's responses were received on 11Apr2019 (Amendment, STN 125694/0.59):

1. Your response to the Question #1 in the CBER IR (dated 14Mar2019) is incomplete. You did not provide the requested information. Please note equipment surfaces that contact sterilized drug

product or its sterilized containers or closures must be sterile so as not to alter purity of the drug product (211.113). In addition, where reasonable contamination potential exists, surfaces that are near the sterile product should also be rendered free of viable organisms. Please update your BLA submission Section 3.2.A.1 to include a description of your procedural controls for the qualification and routine control of (b) (4), as a contract sterilizer for your aseptic filling equipment.

Sponsor's Response: The equipment surfaces that directly contact the sterilized drug product include: the filtered drug product bag and filling needle assembly, which are both sterile single use equipment parts.

Manufacturing filler parts that contact the sterilized containers, vial closures, or are near the sterile products are sterilized prior to use using an (b) (4), a contract (b) (4).

BLA section 3.2.A.1 Facilities and Equipment has been updated to describe the procedural controls and qualification of the (b) (4) at (b) (4). AveXis has the following procedures to control and monitor the (b) (4) at the contract vendor:

- SOP-045 – Supplier Selection and Qualification
- SOP-042 – Supplier Audits
- SOP-288 – Validation Maintenance Periodic Review
- SOP-511 – Sterilization Qualification (Vendor Sites)

On 21 Mar 2019, AveXis conducted a periodic monitoring audit of (b) (4), for its Quality Management System (QMS), and its process(es) for receiving, processing and sterilization of AveXis' equipment parts. There were no findings deemed critical from this audit and additional supplier corrective actions are expected to satisfy AveXis' requirements with regards to SOP and (b) (4) validations. The (b) (4) was found to be acceptable for use.

(b) (4) is registered with FDA, and therefore has undergone inspections by that agency on a regular basis. The most recent general inspection was conducted on (b) (4) and resulted in no 483 observations.

Reviewer's Comments: *The Sponsor's response was accepted.*

2. Your response to the Question #3 in the CBER IR (dated 14Mar2019) is incomplete. You did not provide the requested information. Please address the suitability of your Container Closure Integrity Test method (i.e. CCIT by (b) (4)) to detect the potential compromised container closure integrity due to loss of elastic properties of the CL Butyl stopper (material number (b) (4)) during the long term (up to (b) (4)) storage at  $\leq -60^{\circ}\text{C}$ . **Information provided should address the potential regaining of elastomeric properties of the stopper and the re-sealing of the container closure system once thawed during long term storage.**

Sponsor's Response: AveXis has received additional information from the stopper supplier – (b) (4). The studies performed by (b) (4) have evaluated the container closure integrity of systems comprised of (b) (4) cyclic olefin polymer vials and chlorobutyl stoppers while held at (b) (4). The following reports have been provided

to support this response:

- Container Closure Integrity of Rubber-stoppered Glass and Plastic Vials Stored at (b) (4).
- Performance of (b) (4) Vials at Cryogenic Temperatures: Container Closure Integrity and Cell Preservation.

The chlorobutyl stoppers evaluated in these studies (i.e. formulation (b) (4)) are both manufactured with (b) (4) and have similar glass transition temperatures. Seal integrity of these stoppers was measured by (b) (4)

(b) (4). These stoppers, with the (b) (4) vial and aluminum crimp seal, demonstrated seal integrity while held at (b) (4) storage conditions with no major changes in (b) (4).

The studies performed by (b) (4) support the integrity of the AVXS-101 container closure system while held at the proposed long-term storage condition in addition to container closure integrity performance data summarized in Section 3.2.P.2.4 and 3.2.P.2.5..

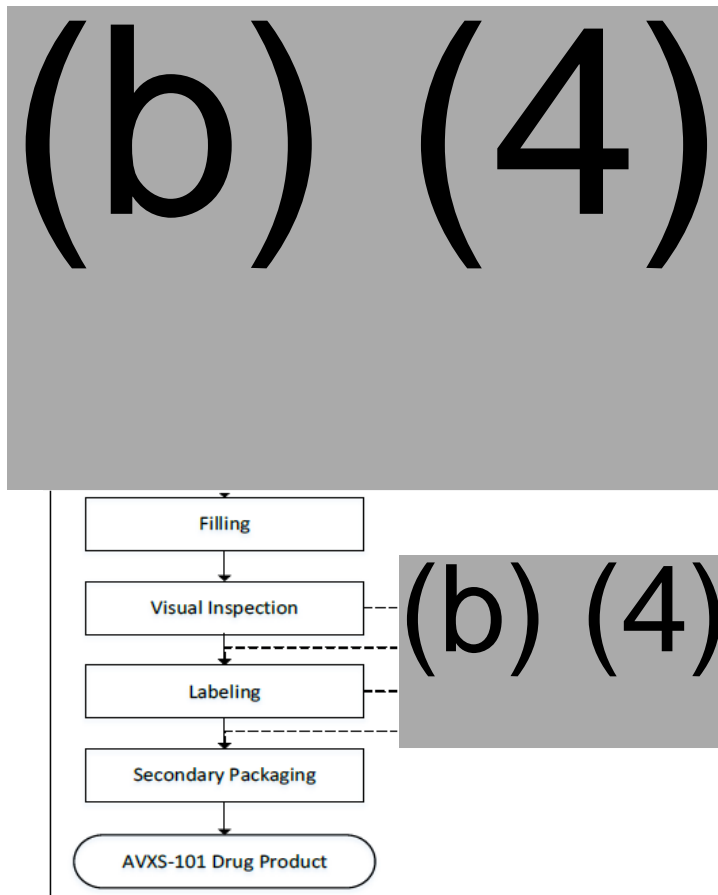
*Reviewer's Comments: The sponsor's response was accepted.*

## IR dated 17Apr2019

Prior to IR dated 17Apr2019, the issue of reprocessing of AVXS-101 DP was covered in 483 Responses Review memo and major updates include:

- In Amendment, STN 125694/0.56 (received on 9Apr2019), the sponsor provided a new (b) (4) SOP-532, indicating possible (b) (4) of AVXS-101 (b) (4) in addition to the (b) (4) of AVXS-101 DP.
- In Amendment, STN 125694/0.60 (received on 11Apr2019), the sponsor revises Section 3.2.P.3.3 by removing the optional (b) (4) of sterile filtered DP. The updated AVXS-101 DP manufacturing process is depicted below in Figure 9. The sponsor also provided a validation summary report (RPT-1320, which was reviewed and accepted by PO reviewer) to support the (b) (4) of AVXS-101 DP under three specific conditions stated in CBRE IR dated 17Apr2019.

Figure 9 The Updated AVXS-101 Drug Product Manufacturing Process



The following requests were sent to AveXis on 17Apr2019 as Inspection related IR. I included this IR and responses here for clarification and conclusion of the (b) (4) issue. The Sponsor's responses were received on 24Apr2019 (Amendment, STN 125694/0.67):

1. Your SOP-532 (version 1.0) is inadequate. The following sections in the SOP-532 (version 1.0) are inconsistent with a statement in Section 3.2.S.2.2 of the original BLA submission, STN 125694/0, which indicates that there are no (b) (4) steps in the AVXS-101 (b) (4) Commercial Manufacturing Process:

"8.1.7 (b) (4) shall only be allowed for:

- 8.1.7.1 (b) (4)

8.1.8 The cumulative impact of (b) (4) steps should be considered prior to a decision to perform a (b) (4) step in a subsequent unit operation. The



acceptability of any (b) (4) batch shall be determined on a case- by-case basis and final disposition resides in the non-conformance report”.

In addition, you have listed (b) (4) required to achieve range criteria” as one of the (b) (4) conditions for (b) (4) in revised Section 3.2.P.3.3 of STN 125694/0.60. We consider this condition for (b) (4) unjustified because adequate control of the (b) (4) Step is an essential requirement for the commercial GMP manufacturing of the AVXS-101 Drug Product.

At this review time-point, the use of a (b) (4) (i.e. the Sterile Filtration (b) (4) step is (b) (4) of AVXS-101 DP) during the AVXS-101 Drug Product manufacturing process is limited by the following conditions:

- Failure of the (b) (4) sterile filter (b) (4).
- Loss of integrity of the (b) (4) the filtered DP and the filling needle.
- Setup issues associated with the filling needle assembly not caused by operator error.

All other (b) (4) conditions would require a pre-approval supplement (PAS). Please acknowledge.

Sponsor’s Responses:

1. AveXis has removed (b) (4) required to achieve range criteria” as a permitted condition for (b) (4).
2. AveXis acknowledges FDA’s clarification on use of (b) (4) for the Sterile Filtration (b) (4) and understands that all other (b) (4) conditions would require a pre-approval supplement (PAS) and FDA approval before any such batch could be dispositioned as released.

***Reviewer’s Comments:*** The sponsor’s responses were accepted. However, the section 3.2.P.3 of STN 125694/0.67 was not updated accordingly.

**IR dated 1May2019**

The following IR items were sent to AveXis on 1May2019, and the Sponsor’s responses were received on 7May2019 (Amendment, STN 125694/0.75):

1. Please update the Section 3.2.P.3.3. by removing (b) (4) required to achieve range criteria” as one of the specific conditions for (b) (4).

Sponsor’s Responses: The sponsor updated section 3.2.P.3 in Amendment (STN 125694/0.75, received on 5/7/2019) by removal of (b) (4) required to achieve range criteria” as a routine (b) (4) condition.

***Reviewer’s Comments:*** The sponsor’s responses are accepted. There is no further question from DMPQ reviewer.

## IR dated 7May2019

The following IR items were sent to AveXis on 7May2019 and were discussed with AveXis on 8May2019 via a teleconference, and the Sponsor's written responses were received on 15May2019 (Amendment, STN 125694/0.81) and on 16May2019 (Amendments, STNs 125694/0.84 and 125694/0.87):

1. During the pre-license inspection (PLI), we audited the summary report of (b) (4) run (b) (4) performed (b) (4). Please provide a summary report of the most recent (b) (4) along with any associated Non-Conformance reports.

Sponsor's Responses: On 8May2019 during the teleconference, the sponsor stated that no (b) (4) study was performed in February 2018 and that the most recent (b) (4) was performed in (b) (4), which was summarized in RPT-1128.

In Amendment, STN 125694/0.81 (received on 15May2019), the sponsor provided RPT-1128 which summarized the (b) (4) as following:

- (b) (4)

In the (b) (4), the (b) (4) FDP hold Time was not included.

Reviewer's Comments: The results of the (b) (4) were found acceptable. Also, as noted in the EIR, the lot (b) (4) was a PPQ DP lot, not a (b) (4) lot,

2. You indicated that the sterile filtered Drug Product (FDP) may be hold for (b) (4). Please provide justifications why your (b) (4) study did not include the (b) (4) hold time.

Sponsor's Responses: During a teleconference (on 8May2019) and in Amendment, STN 125694/0.84 (received on 16/May2019), the sponsor indicated a (b) (4) FDP Hold Time will be challenged in (b) (4).

Reviewer's Comments: The sponsor's proposal of challenging FDP Hold Time in future (b) (4)

studies (b) (4) is acceptable. (b) (5), (b) (7)(E)

3. During the PLI, you indicated that you follow the SOP-170 to clean (b) (4) with sterile (b) (4). Per SOP-170, the minimum contact time for (b) (4) cleaning of equipment surfaces. Your disinfectant effectiveness study indicated that the disinfectant and sporicidal minimum contact times (i.e., (b) (4)) were documented.
- Please describe the procedures for cleaning and sanitizing of (b) (4). Please note that sanitization/disinfection is performed after cleaning.
  - Please provide validation data for the (b) (4) sanitization/disinfection. If validation has not been completed, please provide your plans, including dates for completing this study.

Sponsor's Responses: During a teleconference (on 8May2019) and in Amendment, STN 125694/0.84 (received on 16/May2019), the sponsor stated followings regarding the (b) (4) cleaning:

(a) Cleaning and sanitizing agents:

Per RPT-445 and RPT-904 (Disinfectant Efficacy Study Report) the contact time is (b) (4)

(b) The procedures for cleaning and sanitizing of (b) (4):

- (b) (4)

(c) (b) (4) Cleaning Validation:

- (b) (4) sanitization/disinfection was validated through the Environmental Monitoring Performance Qualification (EMPQ) RPT-333
- Routine and in-operation environmental monitoring is utilized for monitoring effectiveness of sanitization/disinfection

In Amendment (STN 125694/0.81, received on 15May2019), The sponsor provided RPT-445 and RPT-904.

In RPT-445 (31-day aged disinfectant solutions) it was shown that the effectiveness of a sporicidal agent with (b) (4)

- (b) (4)

- (b) (4)

It was noted in RPT-445 that the effectiveness of (b) (4) was not tested on surfaces of (b) (4)

In RPT-904, the effectiveness of (b) (4)

*Reviewer's Comments:* Per SOP-170 (audited during PLI, SOP-170 was uploaded in (b) (4) as an Exhibit (b) (4) a (b) (4) cleaning of equipment surfaces consists of cleaning with a sporicidal solution (b) (4) contact time, followed by (b) (4) disinfectant with a (b) (4) contact time. The sponsor's disinfectant efficacy studies seemed to support the described procedure of (b) (4) sanitization prior to filling. However, while the sponsor stated that routine and in-operation environmental monitoring is utilized for monitoring effectiveness of sanitization/disinfection, it was unclear if EM sampling was performed on (b) (4) and on the filling line surfaces prior and after the cleaning. DMPQ recommends that the (b) (5), (b) (7)(E)

## CONSIDERATIONS (b) (4)

1. The sponsor indicated during a teleconference (on 8May2019) and in Amendment, STN 125694/0.84 (received on 16/May2019) that a (b) (4) FDP Hold Time will be challenged in the (b) (4). DMPQ recommends that verification of (b) (4) study results that support a (b) (4)
2. The sponsor indicated that the effectiveness of (b) (4) sanitization/disinfection is monitored by routine and in-operation environmental monitoring. The procedure, SOP-170 (version 5.0), lacks information in detail for cleaning the surfaces of (b) (4), filler/stopper and gloves. DMPQ recommends that verification of effectiveness of cleaning of surfaces of (b) (4) filler/stopper and gloves (by comparing EM data of (b) (4) surfaces before and after cleaning) (b) (4)

*CBER understands that these recommendations may or may not be taken (based on risk and available resources) and are not requesting documentation to be submitted as evidence of completion.*