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SUMMARY
(BH)

This pre-license inspection (PLI) of the Axevis control testing lab was conducted by the Team Biologics Staff and CBER under BLA STN 125694/0, submitted by AveXis (US License No. 2104) on September 28, 2018 for AVXS-101 (41848A: Pre-license Inspection-Somatic Cell and Gene Therapy). AVXS-101 is proposed for the treatment of pediatric patients with Spinal Muscular Atrophy (SMA).

The AveXis facility located in Libertyville, IL. is the current manufacturing site for the AVXS-101 drug substance and product. Packaging, labeling and filling operations are also conducted at the same facility. The pre-license inspection for that facility was conducted on February 4 - 8, 2019 under FEI # 3012983541. The San Diego AveXis facility, conducts the following relative potency tests for the AVXS-101 drug product:

- Determination of In-vitro Relative Potency for AVXS-101 Drug Product
- Determination of In-vivo Relative potency for AVXS-101 Drug Product

The current pre-license inspection of the control laboratory did not result in a Form FDA 483. However, there were several topics were discussed and are referenced under the “Discussion with Management” section of the EIR. This PLI covered the Quality, Laboratory Control and Facilities and Equipment systems.

There were no refusals during the inspection.

ADMINISTRATIVE DATA

Inspected firm:	AveXis
Location:	10210 Campus Point Dr San Diego, CA 92121-1522
Phone:	646-732-2090
FAX:	
Mailing address:	10210 Campus Point Dr San Diego, CA 92121-1522
Email address:	
Dates of inspection:	2/13/2019-2/15/2019
Days in the facility:	3
Participants:	Burnell M Henry, Investigator - Team Biologics Staff Andrew Byrnes, Ph.D., Supervisory Research Microbiologist – DCGT/ CBER

Andrew Byrnes, Ph.D. and I (Burnell M. Henry) presented our official credentials to Rebecca Clancy Associate Director, QA upon entrance to the firm. This was a team inspection and authorship of sections is indicated by initials (BH, AB).

HISTORY
(BH)

The San Diego AveXis facility is a control testing laboratory. The facility conducts in-vivo and in-vitro relative potency tests for the AVXS-101 drug product.

AveXis, Inc. occupies suite 350 of the 10210 Campus Pointe Dr., San Diego 92121 building on September 13, 2017 as an R&D facility.

On June 01, 2018, the firm occupied suite 300 as the GMP QC laboratory ((b) (4) sq. ft.). GMP preparation activities began at this time and test for GMP method validation was initiated on June 21, 2018.

INTERSTATE (I.S.) COMMERCE
(BH)

This is a control testing laboratory.

JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)
(BH)

This is a control testing laboratory.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED
(BH)

Rebecca Clancy, Associate Director, QA assisted me throughout the inspection with the coordination of facility tours and interviews. AveXis employees provided information and copies of records relating to the Quality, Production and Laboratory Control Systems. Key personnel also accompanied me on the main facility tour as well as individual visits in specific areas during the inspection. Specific personnel and their respective positions are mentioned periodically throughout the EIR for the applicable areas where an additional overview was provided.

MANUFACTURING/DESIGN OPERATIONS
(BH)

The San Diego AveXis facility is a control testing laboratory. The facility conducts in-vivo and in-vitro relative potency tests for the AVXS-101 drug product.

QUALITY SYSTEM
(BH)

My evaluation of Quality System included the review of standard operating procedures and records related to the firm's Quality Assurance personnel responsibilities, investigations, and CAPA's. This facility is a control test laboratory. My review was unremarkable.

Computer and Document Controls

All QC laboratory computers are connected to the GMP network. Access is controlled through the network domain and not through the individual, local domain of the computer. Data archival of QC laboratory data to GMP server was verified. The issuance and control over raw data recording forms is controlled and issued by Quality Assurance. The following protocols were evaluated to verify adequate validation of risk assessments, functional requirement specifications, functional requirement specifications (IQ, OQ, PQ scripts) and calculated potency data from the (b) (4) instrument, which is used for the in-vitro relative potency test.

- SOP-352, entitled, "Use and Operation of (b) (4) " (**Exhibit BH1**)
- RPT-786, entitled, "Installation, Operational & Performances (IQ/OQ/PQ) Report: Validation Summary Report for (b) (4) " (**Exhibit BH2**)
- SOP-238, entitled, "Data Integrity Controls" (**Exhibit BH3**)

My review was unremarkable.

LABORATORY CONTROL SYSTEM

(BH)

I reviewed the Q.C. operations, assay suitability checks on instrumentation for the in-vitro testing, in-vivo relative potency testing, reference standards, finished product COA review, instrument calibration program and environmental monitoring. The following protocols were evaluated during my assessment.

- SOP-124, entitled, "Management of the AveXis Calibration Program" (**Exhibit BH4**)
- SOP-285, entitled, "Determination of In-vivo Relative Potency for AVXS-101 Drug Product" (**Exhibit BH5**)
- SOP-346, entitled, "In-vivo Functionality Test using a Single Dose AVXS-101 in SMNA7 Mouse Model" (**Exhibit BH6**)
- SOP-347, entitled, "Determination of In-vitro Relative Potency for AVXS-101 Drug Product" (**Exhibit BH7**)

My review was unremarkable.

Personnel Training

The firm utilizes written procedures SOP-302, entitled, "GMP Site Training Procedure" (**Exhibit BH8**) and SOP-069, entitled, "QC Training Qualification" (**Exhibit BH9**) to monitor training at this facility.

The Learning Management System (LMS) manages the assignment of training activities and the creation or update to any content regarding training activities. Employees receive GMP training approximately (b) (4) . Depending on the job description, additional training in the respective area is also provided. Training records were verified for individuals involved in manufacturing, quality assurance and other operations regarding the manufacture of the AVXS-101 drug product. My review was unremarkable.

Laboratory Investigations

SOP-080, entitled, "OOS/OOT Laboratory Investigation" (**Exhibit BH10**) describes the procedure for handling out of specification (OOS) and out of trend (OOT) laboratory results. Laboratory investigations are required in response to valid, OOS and OOT laboratory results. The laboratory investigation is a systematic and in-depth documented evaluation of the materials, events, and actions surrounding test results that do not meet a specification. My review of the laboratory out of specification investigations was unremarkable.

(AB)

In vivo potency assay, SOP-346

On 2/13/19, we toured the vivarium with Taryn Cozine, (b) (6) and Allan Kaspar. The in vivo potency assay SOP-346 is performed in (b) (4)

I reviewed SOP-346 v2.0 (In-vivo functionality test using a single dose AVXS-101 in SMNΔ7 mouse model). This version of the SOP went into effect on 1/10/19. The SOP was modified to add new forms for documentation and to clarify and standardize (b) (4)

I also reviewed several supporting protocols for the in vivo potency assay (SOPs for genotyping, i.v. injection, breeding and mouse observation), including SOP-266 (General mouse colony maintenance and breeding). SOP-266 does not have any procedures to prevent long-term genetic drift of the colony. I noted as a discussion item at the

morning daily summary on 2/14/19 that the firm should consider procedures to minimize genetic drift by, for example, periodically re-starting the colony from cryopreserved embryos every 3-5 years, or backcrossing onto wild-type mice.

I reviewed RPT-859 v2.0 (Method validation report for SOP-346, based on PRO-529 validation plan). I reviewed the original records for this validation report. The in vivo potency assay was run with (b) (4) groups ((b) (4) control and lots AAV9SMN0613, 600443 and 600629). Version 1.0 of RPT-859 was submitted in the BLA. Version 2.0 is dated 2/7/19 and corrects multiple errors in the report, including the addition of a mouse to the AAV9SMN0613 group (the mouse was inadvertently omitted in the first version of the report), (b) (4) decrease in survival time for one mouse in the AAV9SMN0613 group, and change in the status from alive to dead for (b) (4) mice in the 600629 group. I verified in the original records that the new information in RPT-859 v2.0 was correct. The errors in RPT-859 v1.0 were the result of poor record keeping using non-validated forms (see other NCRs/CAPAs). I determined that the errors have no negative impact on the conclusion that assay SOP-346 is validated. In discussion with Shannon Lindberg, I noted that the incorrect validation report RPT-859 v1.0 needed to be updated in the BLA, and she agreed. In daily summary discussion on the afternoon of 2/14/19, I noted that the change to this validation report had only been finalized on 2/7/19 and therefore it was understandable that the BLA had not yet been updated with the correct version of this report, but this incident and other incidents at the San Diego and Libertyville sites highlight the need for managed documents such as RPT-859 to be updated in the relevant BLA or IND submission when errors are discovered or major changes are made. The firm agreed to update the BLA with the new version of RPT-859 and to provide a plan for improvement of their regulatory submission of managed documents.

I reviewed four additional test reports for the in vivo potency assay SOP-346 (DP lots 601182, 601183, 601436 and 601437). I reviewed records of genotyping, weight recordings, and survival times. As noted in NCR-1352, the mice for the 601436 and 601437 groups were erroneously injected with (b) (4) vector than intended ((b) (4)% and (b) (4)% of the intended amount, respectively), but these lots still met the specification of (b) (4) days median survival. I noted that weights are recorded only (b) (4) (b) (4) (rather than daily), which frequently leads to bunching of survival times when survival is based on body weight loss. This practice of weighing only (b) (4) is acceptable, with no major impact to the assay.

I reviewed NCR-1116 (DOC-Incorrect: Data reported in REC-1606 contains discrepancies). This NC was discovered on 10/11/18 and closed 1/28/19. Corrective actions are described in CAPAs 308, 418, 420 and 421. NCR-1116 describes errors discovered in AveXis reports when reviewing mouse survival data from the old in vivo potency assay (SOP-285), and these errors triggered an extensive investigation, including reviewing all of the original records of experimental mice for SOP-285 and SOP-346. We were already aware (through BLA amendment 4) of the problems and their resolution, and we have already performed an independent analysis of the corrected survival data that were

submitted to the BLA in REC-1606. The in vivo potency assay was originally conducted at (b) (4) (b) (4) (before the establishment of SOP-285), and the assay was then transferred to AveXis San Diego when their animal facility opened in 2018. SOP-285 has recently been replaced with SOP-346. The root cause of the errors was using a non-validated spreadsheet to calculate the data. Additional contributory factors were difficulty in obtaining accurate data from (b) (4), and QA not properly verifying calculations. The corrected data included changes to survival times (resulting from unclear definition of the date of birth), which had minor impact on the calculated in vivo potency for lot 816836 (see NCR-965). Three of the (b) (4) mouse records had to be excluded completely because of errors. Appropriate action has been taken to restate results, to validate the spreadsheet, and to improve QA review.

NCR-965 (Lab-DOC: Discrepancy discovered for the median survival at the (b) (4) vg/kg dose for relative potency testing for DP lot 816836). This NC was raised on 8/23/18 and closed on 9/20/18. We were already aware of this correction through the BLA. The potency for lot 816836 (determined by SOP-285) was recalculated from the original incorrect value of 103% to the correct value of 100%. Both values are within the release specification (at the time) of (b) (4)%.

CAPA-308 (Revise SOP-285, SOP-266 and SOP-268 to clarify formula for days of survival and documentation activities). SOPs were improved to clearly define the day of birth, so that the survival times can be calculated correctly. SOP-285 is now obsolete (replaced by SOP-346). I verified appropriate corrections in SOPs 266 and 268.

CAPA-418 (GDP training). This CAPA describes retraining of AveXis San Diego analysts on good documentation practices. This CAPA includes a (b) (4) effectiveness check EC-12 to evaluate whether the actions were effective at reducing the number of GDP errors in the in vivo potency assay. In addition to retraining of analysts, QC will perform (b) (4)% review of data from Form-212 for the in vivo potency assay, and QA will audit approximately (b) (4)% of the records and conduct a review to determine effectiveness and whether any additional actions are necessary.

CAPA-420 (Restate affected results). This CAPA covers updates to REC-1606 and other documents to correct mistakes discovered in NCR-1116.

CAPA-421 (Review all data generated by in-vivo). Ongoing review of all in vivo survival data, including the validation report for SOP-346, which resulted in correction of the validation report RPT-859 on 2/7/19. I discussed with the firm that the updated version of RPT-859 should be submitted to the BLA.

I reviewed REC-1070 v2.0, which had previously been submitted to the BLA in amendment 28. I noted that version 1.0 of REC-1070 had previously been submitted to IND 15699. REC-1070 is a simulation study to help to determine assay cut points for SOP-346. It was unclear what the differences were between v1.0 and v2.0. I verified with Fengrong Zuo that REC-1070 v2.0 had been updated with the

corrected survival data and reanalyzed by the statistician. Thus, the BLA contains the corrected version of this study.

In vitro relative potency assay, SOP-347

On 2/14/19, we viewed SOP-347 data acquisition from (b) (4) prepared by R&D (a mock assay). Data acquisition was performed by (b) (6). The demonstration included data acquisition using the (b) (4), and data analysis using (b) (4) software. The (b) (4) was (b) (4) for approximately (b) (4) on the (b) (4) using a locked protocol. Data were transferred by exporting to a CSV file format, which was then transferred to the locked Q: drive. Data were then copied and pasted into a locked (b) (4) spreadsheet that performs all system suitability checks and data analysis. Final relative potency values are calculated by (b) (4) independent runs on (b) (4) independent (b) (4) (this part was not included in the demonstration).

I reviewed the validation protocol PRO-573 for the in vitro potency assay SOP-347, including original test reports. These data are the basis for the assay validation report RPT-863, which has already been reviewed in the BLA. I verified that the entire validation study was performed with lot 600443. I did not note any concerns.

LI-119 (LAB-OOS: Out of specification for DP in vitro relative potency for lot 601533) is an open investigation for a result of 67% in the in vitro potency assay SOP-347. This result is outside the acceptance criteria of (b) (4)%. This OOS occurred on 1/29/19, and the investigation is still ongoing with a due date of 2/28/19. No decision has been reached about lot disposition. This is the first OOS for SOP-347. No laboratory error has been identified so far, and other samples that were run on the same (b) (4) were within specification.

Establishment of vector reference standards

On 2/14/19 I discussed with Jim L'Italien, Craig Seddon, Lynne Martin and Mark Roache about procedures for establishing vector reference standards, and about problems that they had encountered when changing (b) (4)

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Documentation Errors

I reviewed NCR-1352 (DOC – Incorrect: Discrepancy on FORM-328 – Incorrect titer value), which occurred on 11/7/18 and was discovered on 12/21/18 during review of the release data. For two lots of DP, the in vitro and in vivo potency assays were mistakenly performed using the nominal vector concentration (e.g., (b) (4) vg/mL) rather than their actual concentrations ((b) (4) vg/mL for lot 601436, and $1.9x10^{13}$ vg/mL for lot 601437). As a result, too little vector was used in these assays. However, both lots met specifications, and thus there was no impact. Interviews with analysts determined that it had long been their practice to use the nominal vector concentration rather than the actual vector concentration, and therefore the investigation was expanded to include additional assay results that had incorrectly used the nominal vector concentration. There was no impact to the in vivo potency assay (likely due to the insensitivity of this assay). There was also no impact in the in vitro potency assay – all results remained within specification, even though the amounts of vector used had varied between (b) (4)% and (b) (4)% of the amount that should have been used. When the results of the in vitro potency assay are corrected for this discrepancy, they still remain within specification, and thus there is no impact. CAPA-465 (current status: QA final approval) will correct the problem by updating all SOPs to require that the actual vector concentration be obtained from a CoT or CoA before initiating testing. I also reviewed several invalid/aborted assay reports for the in vitro potency assay (IAA-280, IAA-281, IAA-284) that all occurred during the same assay run on Nov. 9-13, 2018, around the same time that this problem was discovered. One assay was invalidated and two were aborted because they were using the nominal vector concentration, not the actual vector concentration.

Additional Review

General procedures for quality control, sample management, OOS/OOT investigation, aborting/invalidating assays, etc., are identical between the AveXis Libertyville and San Diego sites. These procedures were evaluated during the inspection of AveXis Libertyville.

I reviewed RPT-1113 regarding whether different vials of a single DP lot have uniform strength and (b) (4) concentration. This report was based on PRO-579, and the purpose was to verify that the change in fill volume to 5.5 mL and 8.3 mL did not affect the uniformity of the fill. The first and last vials of DP lots 601182 and 601532 were assayed for strength by (b) (4) and (b) (4) concentration by (b) (4) There were no significant differences between the first and last filled vials, demonstrating that filling was uniform.

I reviewed SOP-315 v3.0 (Processing CMC regulatory submissions in (b) (4)). This SOP contains procedures for authoring and reviewing a document for regulatory submission. Quality performs a review for major errors, including a partial random audit of the data, before sending the documents to Reg Affairs for submission. SOP-315 does not include any procedures to trigger updating of the regulatory submission if errors are later discovered in the document. This issue was a discussion item

on the afternoon of 2/14/19, and we advised the firm that they should improve their procedures for updating BLAs and INDs for managed documents, when these documents or their underlying data change materially. The firm agreed to provide an amendment to the BLA updating their procedures.

FACILITIES AND EQUIPMENT SYSTEM
(BH)

This facility is a control laboratory and currently conducts the relative potency tests for the in-vitro and in-vivo tests for the AVXS-101 drug product. I reviewed standard operating procedures, records, and practices related to facility layout, air handling systems, preventive maintenance/calibration of equipment, and the Supervisory Control and Data Acquisition (SCADA) System. SOP-232, entitled, "Operation of the SCADA System" (**Exhibit BH11**) and SPEC -123, entitled, "6111, 4113, 4114 AVXS-101 (b) (4) " (**Exhibit BH12**) were evaluated to verify storage conditions for the AVXS-101 drug product.

SCADA quality alarms freezer (60°C) deviations were reviewed through the SCADA system to access the communication and monitoring of the AVXS-101 drug product storage units. My request for the quality alarms was specifically for the drug product storage freezers. The quality alarm response times documented in the deviation reports were acknowledged in a timely manner and root causes were identified. The AVXS-101 drug product storage conditions are adequate, and my review was unremarkable.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE
(BH)

There were no objectionable conditions noted.

GENERAL DISCUSSION WITH MANAGEMENT
(AB)

1. FDA recommended that the firm develop a plan for long-term mouse colony management to minimize the impact of genetic drift in the SMNA7 mice.
2. FDA asked the firm to develop procedures to ensure that managed documents are promptly updated in regulatory submissions, when needed. The firm agreed to update their procedures and to submit the updated procedures to the BLA along with any managed documents that need to be updated in the BLA.

3. FDA noted that (b) (4) reference standard RS-002 had not been (b) (4)

EXHIBITS COLLECTED
(BH)

Exhibit BH1: SOP-352, entitled, "Use and Operation of (b) (4) " (12 pages)
Exhibit BH2: RPT-786, entitled, "Installation, Operational & Performances (IQ/OQ/PQ) Report: Validation Summary Report for (b) (4) " (10 pages)
Exhibit BH3: SOP-238, entitled, "Data Integrity Controls" (7 pages)
Exhibit BH4: SOP-124, entitled, "Management of the AveXis Calibration Program" (10 pages)
Exhibit BH5: SOP-285, entitled, "Determination of In-vivo Relative Potency for AVXS-101 Drug Product" (11 pages)
Exhibit BH6: SOP-346, entitled, "In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model" (8 pages)
Exhibit BH7: SOP-347, entitled, "Determination of In-vitro Relative Potency for AVXS-101 Drug Product" (41 pages)
Exhibit BH8: SOP-302, entitled, "GMP Site Training Procedure" (10 pages)
Exhibit BH9: SOP-069, entitled, "QC Training Qualification" (6 pages)
Exhibit BH10: SOP-080, entitled, "OOS/OOT Laboratory Investigation" (14 pages)
Exhibit BH11: SOP-232, entitled, "Operation of the SCADA System" (23 pages)
Exhibit BH12: SPEC -123, entitled, "6111, 4113, 4114 AVXS-101 (b) (4) " (4 pages)

ATTACHMENTS

FORM FDA 482

Signature page:

Burnell M. Henry -S

Digitally signed by Burnell M. Henry -S
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Date: 2019.04.09 10:59:14 -04'00'

Burnell M. Henry, Investigator
OBPO / Team Biologics Staff

Andrew P. Byrnes -S

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