

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 19701 Fairchild Irvine, CA 92612-2445 (949) 608-2900 Fax: (949) 608-4417		DATE(S) OF INSPECTION 7/24/2019-8/2/2019*
		FEI NUMBER 3014617030
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Mr. Mark P. Roache, Senior Vice President and Chief Quality Officer		
FIRM NAME AveXis, Inc.	STREET ADDRESS 10210 Campus Point Dr Ste 300	
CITY, STATE, ZIP CODE, COUNTRY San Diego, CA 92121-1522	TYPE ESTABLISHMENT INSPECTED Control Testing Lab	

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

## OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

A. Non-conformance Report NCR-1922 (which was open at the time of the current inspection) was opened on 15 May 2019 due to a report that was made to the CQO (Chief Quality Officer) alleging that data derived from the AVXS-101 In-Vivo Relative Potency Assay Studies 1-10 may have been mismanaged or even potentially manipulated. Aside from evaluations of Studies 1-10 and a planned evaluation of toxicological studies under NCR-2018 there is no documentation in this NCR that an audit of all other potentially impacted data, studies, and reports was conducted or is planned to determine if there was evidence of data mismanagement or manipulation or a justification for not conducting or planning such an audit. Additionally, there is no documentation in NCR-1922 as to why the NCR was not opened until 15 May 2019 when the initial allegation is documented as having been reported on 14 March 2019.

B. Non-conformance Report NCR-409 was opened on 31 Jan 2018 and has an “Event Description” of “On 31Jan2018, during a historical data review of the potency results for Drug Product Lot 600156 per SOP-285, Determination of In Vivo Relative Potency for AVXS-101 Drug Product, it was discovered that the associated assay form (FORM-212) was not completed at the time of CoA generation and approval for Lot 600156....” During the inspection, the associated FORM-212 was reviewed and it was observed that the date/time stamps on the 4 page form are discrepant in that 3 of the 4 pages have a “Generated” date/time of “05 Jan 2018 09:44AM” and 1 page (page 2) has a “Generated” date/time of “04 Jan 2018 09:39AM”. There is no documentation in NCR-409 that this discrepancy was noticed or investigated. Additionally, current SOP-381 Version 2.0 entitled “Control of QC Test Forms” does not specifically require verification of consistent date/time stamps on each page of a test form during reconciliation of the form.

<b>SEE REVERSE OF THIS PAGE</b>	EMPLOYEE(S) SIGNATURE  Scott T Ballard, Investigator Mihaly S Ligmond, Investigator - Team Biologics	DATE ISSUED  8/2/2019
	 Scott T Ballard Investigator Signed By Scott T. Ballard -S Date Signed 08-02-2019 12 49 13 <b>X</b>	

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C. Non-conformance Report NCR-965 was opened on 23 Aug 2018 and has and “Event Description” of “On 23Aug 2018, during the review of  $\Delta$ 7SMA mouse database, it was discovered that there were discrepancies in the data that was used to calculate relative potency for AVXS-101 Drug Product. Lot 816836 had single mouse survival days recorded that were different from the actual value....” As documented in the investigation most of the discrepancies noted were discrepant by a single day which was attributed to ambiguity in SOP-285 “Determination of In-Vivo Relative Potency for AVXS-101 Drug Product” however in 4 cases discrepancies of greater than 1 day were noted (ranging from 2-19 days). There is no documentation in NCR-965 that these 4 cases were investigated further to determine a potential root cause.

D. Non-conformance Report NCR-1116 was opened on 15 Oct 2018 and has “Event Description” of “Inconsistencies were identified during the review and approval of the data previously reported within REC-1606 v1.0 ‘Mouse Survival Data: Results for In-vivo Relative Potency for AVXS-101 Drug Product’....” As documented in the investigation “...During investigational review of the Quality Employee’s process, it was determined that some of the early raw data results were initially communicated verbally from the...to the AveXis Quality Employee....” There is no documentation in NCR-1116 explaining why the Quality Employee accepted verbal communication of raw data without corresponding written documentation.

## **OBSERVATION 2**

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

- A. Analytical Balance ID #: (b) (4) which is used to weigh mice handled under SOP-268 Version 2.0 entitled “Observation and Handling of Study Mice for AVXS-101 Potency Assay” does not have audit trail capability. These mice are used for SOP-346 Version 3.0 entitled “In-vivo Functionality Test using a Single Dose AVXS-101 in SMN $\Delta$ 7 Mouse Model.”
- B. Printouts for the weighing of mice are not made and included in the logbook where the weights are currently manually recorded. Analytical Balance ID #: (b) (4) which is used to weigh the mice is capable of producing printouts of weighings; however printouts of mouse

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weights are not made and included with the data that is manually recorded in the logbook, that as an example can be seen in Logbook ID Number 000139 “AVXS-101 In-vivo Functionality” on FORM-339 “Weight and Survival Data for AVXS-101 Functionality Test”. These mice are used for SOP-346 Version 3.0 entitled “In-vivo Functionality Test using a Single Dose AVXS-101 in SMN $\Delta$ 7 Mouse Model”.

C. The equipment number of the analytical balance which is used to weigh mice handled under SOP-268 Version 2.0 entitled “Observation and Handling of Study Mice for AVXS-101 Potency Assay” is not recorded in the logbook which, as an example can be seen in Logbook ID Number 000139 “AVXS-101 In-vivo Functionality”. These mice are used for SOP-346 Version 3.0 entitled “In-vivo Functionality Test using a Single Dose AVXS-101 in SMN $\Delta$ 7 Mouse Model”.

### OBSERVATION 3

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, vivarium employees who have responsibilities for GMP functions such as animal dosing, tail snips for genotyping, weighing, death determination, and contemporaneous documentation report directly to an R&D manager. This is not in accordance with the "Quality Manual" version 3. There are (b)(4) employees that perform these functions for commercial product testing (SOP-346 - In-vivo Functionality Test using a Single Dose AVSX-101 in SMNΔ7 Mouse Model) who directly report and are supervised by a "Senior Scientist" in the Research and Development team. This Senior Scientist has self-described no direct prior experience in GMP controlled lab work.

## OBSERVATION 4

Laboratory records do not include complete records of any testing and standardization of laboratory reference standards.

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		8/2/2019
		<p>Scott T Ballard          Investigator          Signed By Scott T. Ballard -S          Date Signed 08-02-2019 12:49:13</p> <p>X</p>

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Specifically, reference standard lots have not been tested and shown to meet initial release criteria in applicable versions of SOP-285 (Determination of In Vivo Relative Potency for AVXS-101 Drug Product) such as minimum slope of increasing doses, minimum mouse cohort sizes, and minimum survivability medians at the test dose.

This is applicable to reference standard lots #AAV9SMN0613 and #600443 tested in March 2017 and February 2018 respectively which serve as reference standards for potency and in-vivo functionality methods performed for the AVXS-101 product over the past three years. These lots have potency values reported in BLA 125694.

## **OBSERVATION 5**

Established test procedures are not followed.

Specifically, as per SOP-346 Version 3.0 “In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model” the mouse date of death is in part defined as the “...date the animal first lost <sup>(b)(4)</sup>% of its body weight...”. As per SOP-268 Version 2.0 “Observation and Handling of Study Mice for AVXS-101 Potency Assay” study animals are weighed “...(b) (4) (separated by at least (b) (4) ) until end of study...” AveXis has interpreted the date the animal first lost <sup>(b)(4)</sup>% of its body weight as the date this loss is first documented. Since mice are not weighed daily there is no documentation showing the exact date the mouse lost <sup>(b)(4)</sup>% of its body weight.

## **\*DATES OF INSPECTION**

7/24/2019(Wed), 7/25/2019(Thu), 7/26/2019(Fri), 7/29/2019(Mon), 7/30/2019(Tue), 7/31/2019(Wed), 8/01/2019(Thu), 8/02/2019(Fri)

Mihaly S Ligmond  
Investigator - Team Biologics  
Signed By: Mihaly S. Ligmond -S  
Date Signed: 08-02-2019 12:50:23

<b>SEE REVERSE OF THIS PAGE</b>	EMPLOYEE(S) SIGNATURE Scott T Ballard, Investigator Mihaly S Ligmond, Investigator - Team Biologics	DATE ISSUED 8/2/2019
	<i>X</i>	

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."