

**From:** [Jarvis, Candace](#)  
**To:** [James L'Italien, PhD \(jlitalien@avexis.com\)](#)  
**Cc:** [Jarvis, Candace](#); [Byrnes, Andrew](#); [Nancy Boman](#)  
**Subject:** BLA 125694/0| AveXis, Inc| Information Request 17 (PLEASE RESPOND BY JANUARY 22, 2019)  
**Date:** Thursday, December 20, 2018 1:57:26 PM  
**Attachments:** [image013.png](#) **Importance:** High

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Good afternoon Dr. L'Italien

We have the following CMC request for information for BLA 125694. Please respond to this request by no later than January 22, 2019.

1. Regarding justification of specifications, the data for the following parameters do not appear to fit normal (Gaussian) distributions: (b) (4) DNA (b) (4) (b) (4) DP). If data are not normally distributed, then it is not appropriate to base acceptance criteria on standard deviations or tolerance intervals for normal distributions. Please propose appropriate acceptance criteria for these parameters and provide sufficient justification for the approach to calculating these acceptance criteria.
2. The rationale for setting the limits at (b) (4) LOQ for protein impurities (b) (4) (b) (4) is not sufficient. The levels of these protein impurities in (b) (4) has never exceeded the LOQ of these assays. Unless you are able to provide adequate justification, you should set a limit of < LOQ for each of these assays, without a multiplicative factor and without (b) (4) to (b) (4) (b) (4). For example, for (b) (4) the acceptance criterion should be (b) (4) assay).
3. Please provide the report that generated the data for 3.2.S.3 (Characterization) sections 1.3 and 1.4.
4. Regarding the acceptance criteria for % Total Impurities by (b) (4) (SOP180), please explain what the word "related" means in "no single unnamed related impurity" and "named related impurities." If the meaning is that these impurities are process-related or product-related, please provide the evidence for this claim.
5. Regarding your (b) (4) assay (SOP-263) and validation of this assay, please respond individually to each of the points below:
  - a. The number of informative (b) (4) (usable (b) (4) that contain information about AAV (b) (4) is a critical parameter that impacts the quality of the assay output. The number of informative (b) (4) (b) (4). Although

the (b) (4) has remained constant throughout the development of your assay, the (b) (4) and the (b) (4) have changed. Because of these changes, we are concerned that SOP-263 version 3.0 might have meaningful differences from the assay versions that were validated in RPT-592 and RPT-640. Please clarify the following issues and, if needed, take appropriate action:

- i. The number of (b) (4) for RPT-640 and RPT-592 were 1 and 3, respectively. The number of informative (b) (4) in RPT-640 appears to be approximately (b) (4). SOP-263 version 3.0 indicates that (b) (4) per sample. This suggests that the number of informative (b) (4) in SOP-263 version 3.0 would only be about half the number seen in RPT-640 (assuming no other differences in parameters such as (b) (4)).
1. Please explain why the number of (b) (4) is different between SOP-263 version 3.0 and the validation runs, and explain how this difference affects assay performance, especially precision and LOQ.
2. Please explain whether the number of informative (b) (4) generated by SOP-263 version 3.0 is in alignment with our previous recommendation under IND 15699 that there be (b) (4) usable (b) (4).
- ii. The number of (b) (4) for RPT-640, SOP-263 version 3.0 and RPT-592 were (b) (4) and unclear, respectively. RPT-691 indicates that the (b) (4) could be improved to as low as (b) (4) issue is fixed. CCR-198 seems to indicate that the (b) (4) issue has been fixed. Please clarify whether fixing this issue will allow you to improve the (b) (4).

b. Test articles are run in (b) (4) in SOP-263 version 3.0, but it is unclear how the results are averaged. Please clarify.

c. (b) (4) is listed in the BLA as a DP release test site for the (b) (4) assay. Although you have evaluated reproducibility between the (b) (4) and AveXis (b) (4) sites, it is unclear which versions of the assay were used to generate the data in RPT-592 and RPT-640, and it is unclear which version of the assay will be implemented at (b) (4) for the license.

- i. Please provide copies of the versions of SOP-263 that were validated in RPT-592 and RPT-640.
- ii. Section 2 of SOP-263 version 3.0 is vague regarding which SOP will be followed at (b) (4) for DP lot release.

Please clarify and please provide Attachment 1 from SOP-263 version 3.0.

- d. The assay validations were performed at confidence level (b) (4), but SOP-263 version 3.0 allows an (b) (4) of either (b) (4). The criteria for selecting the appropriate (b) (4) for data analysis in SOP-263 are unclear, and the impact of changing the (b) (4) was not sufficiently analyzed during assay validation. If you wish to use (b) (4), you will need to validate the assay using (b) (4). You will also need to provide clear criteria for selecting the appropriate (b) (4) in SOP263. Please comment.
- e. Your (b) (4) data appear to have significant variability from run to run in (b) (4). Please analyze this variation and set appropriate ranges for (b) (4) as assay acceptance criteria in SOP-263.
- f. SOP-263 section 10.3.6 indicates that (b) (4) may be performed in some cases, and that (b) (4) will follow the process in SOP-282. Please clarify in SOP-263 under what circumstances (b) (4) may be used, and please provide SOP-282.
- g. In SOP-263 section 11.1, what exactly are the system suitability criteria?
- h. Please describe how you will handle potential future version updates of (b) (4) software.
- i. We will not be ready to discuss the acceptance criteria for the (b) (4) assay until after resolution of the issues above and issue #7 from our 10/28/18 letter. However, at this stage we would like to note the following points regarding acceptance criteria for this assay:
  - i. In general terms, we agree with your approach to controlling the (b) (4) and other (b) (4). This approach is preferable to controlling the (b) (4) alone.
  - ii. (b) (4) of the (b) (4) lots used to justify the specification for this assay in 3.2.P.5.6.14 were analyzed with an (b) (4) of (b) (4), while the other (b) (4) lots were analyzed with an (b) (4) of (b) (4). As noted above, it appears that use of the (b) (4) has not been

validated, and therefore it is unclear whether it is appropriate to (b) (4) lot release results that were generated using these different (b) (4)

iii The first (b) (4) of the (b) (4) lots used to justify the specification for

this assay in 3.2.P.5.6.14 have high levels of (b) (4) due to inadequate control of the (b) (4) step of the manufacturing process (b) (4)-673). Manufacturing process control was improved after the (b) (4) lot, and as a result the last (b) (4) lots have much lower (b) (4) percentages. The (b) (4) lots are not representative of the levels of (b) (4) that will typically be achieved by the current manufacturing process, and therefore it does not seem appropriate to consider these (b) (4) lots when setting acceptance criteria for this assay.

iv Given the limited number of lots available with the current (better-controlled) manufacturing process, we may be willing to consider setting the (b) (4) acceptance criterion to a level that is no worse than lot (b) (4). In this circumstance, we would expect your continued process verification plan to include a detailed strategy for revising the acceptance criteria once you have additional manufacturing experience. It is understood that any revision to acceptance criteria after licensure would require submission of a PAS.

Please let me know if there are any questions.  
Please acknowledge receipt.

*Regards,*

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