

From: [Jarvis, Candace](#)
To: [James L'Italien, PhD \(jlitalien@avexis.com\)](#)
Cc: [Nancy Boman](#); [Jarvis, Candace](#); [Byrnes, Andrew](#)
Subject: BLA 125694/0| AveXis, Inc| Information Request 23 (PLEASE BY February 15, 2019)
Date: Monday, January 07, 2019 10:18:06 AM
Attachments: [image013.png](#) **Importance:** High

Good morning Dr. L'Italien and Happy New Year,

We have the following request for information for BLA 125694/0. We ask that you respond to this email by February 15, 2019. Should you not be able to meet this deadline, please let us know as soon as possible.

Comments:

1. There are no data characterizing the ability of your manufacturing process to clear (b) (4) is toxic by the i.v. route and could detrimentally affect the safety of your product if it were present as an impurity in DP. The theoretical discussion of (b) (4) clearance in 3.2.S.3.2.2.5 assumes a (b) (4) of (b) (4) during (b) (4), and assumes that (b) (4) does not form complexes that are larger than the cutoff of the (b) (4) is a (b) (4) that is known to form (b) (4) under some conditions, and it is possible that it may associate with cells, cellular debris, DNA, vector or product-contact surfaces in unpredictable ways that impede its removal. Please provide process clearance studies for (b) (4) or data demonstrating negligible concentrations of (b) (4) in (b) (4).
2. Regarding the total protein by (b) (4) assay (SOP-184); the validation of this assay (RPT-472); the protein acceptance criteria for DP release; and lot release results generated by this assay, please address the following issues:
 - a. (b) (4) produces a strong positive reaction in (b) (4) assays (b) (4). Because clearance of (b) (4) has not been evaluated for your manufacturing process and because the concentration of (b) (4) in DP is unknown, there is insufficient validation that SOP-184 is specific for protein in your product. This issue should be addressed either by demonstrating that your manufacturing process robustly clears (b) (4) or by data demonstrating that (b) (4) concentrations in DP are below levels that will interfere with the ability of the (b) (4) assay to specifically measure protein concentration.
 - b. The variance among DP lots in 3.2.P.5.6.7 seems too wide. Likewise, the proposed acceptance criterion of (b) (4) seems too wide. We previously communicated a concern about the width of this

specification in an email on October 6, 2017 under IND 15699. Validation report RPT-472 indicates that SOP-184 is a very precise assay (intermediate precision RSD (b) (4)), but the lot release results reported in 3.2.P.5.6.7 have notably higher variance (RSD (b) (4)), suggesting that most of the variance is due to the product, rather than the assay. Data from other assays that measure protein impurities (b) (4) do not support the idea that there are highly variable levels of protein impurities. Together, these data suggest either the presence of substantial amounts of unidentified protein impurities that can only be detected by SOP-184; or the presence (in some lots) of substantial amounts of an unidentified non-protein impurity that is detected by the (b) (4) assay; or much higher than expected imprecision in results from SOP-184.

- c. The results reported in 3.2.P.5.6.7 call into question whether all of the AveXis lots are comparable to lot (b) (4) (which has (b) (4)). Our agreement on comparability at the pre-BLA meeting was based on the data that were available at the time (up to (b) (4) for the AveXis lots). The upper end of the data range reported in 3.2.P.5.6.7 (up to (b) (4)) is (b) (4) higher than the value for AAV9SMN0613, suggesting a lack of comparability.

Please acknowledge receipt of this email.

Regards,

Candace N. Jarvis

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