

From: Trayer, Amanda
Sent: Wednesday, March 27, 2019 10:32 AM
To: 'Jlitalien@avexis.com'
Cc: Wang, Wei (FDA); Trout, Deborah; Jarvis, Candace
Subject: Information Request for BLA 125694/0

Dr. L'Italien-

We have following questions. Question #1 is regarding the off-site storage facility, and Questions 2 – 5 are generated from the review of the 483 responses. We expect to receive the responses by 8Apr2019 in Gateway. Thank you.

1. 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.

2. We noted that in your response to the Observation 11 (Amendment STN 125694/0.48, received 20Mar2019), you did not indicate when a written SOP for reprocessing processes (as per 21CFR211.115) will be drafted or completed. Please provide the reprocessing SOP.

In addition, we consider the Section 8.9 of your SOP-303 (Drug Product Thaw and Sterile Filtration) inadequate. Please revise the section by referencing an adequate (b) (4) SOP.

3. We agree with you on the (b) (4) of the Filtered Drug Product (FDP) due to potential risks to the drug product sterility caused by mechanical failures (i.e. Failure of the (b) (4) sterile filter (b) (4) test, Failure of (b) (4) the FDP bag and the filling needle, and mechanical failure of the filling needle assembly). However, we cannot prospectively approve (b) (4) as a routine corrective action to address human error-related events. In case you do need to (b) (4) FDP due to human errors caused non-conformances (including human errors in setup the fill needle assembly, and needs of further (b) (4)), you may follow the 21CFR 610.9 to request the FDA approval for releasing the affected DP lots post approval.

4. The response to observation 1 does not contain sufficient information to evaluate whether the response is adequate. Please provide the following:

- a. SOP-488
- b. A list of the assay standard reference materials covered by SOP-488
- c. Please clarify whether SOP-488 overlaps with SOP-326 (Establishing assay controls in the QC laboratory), and clarify how SOP-488 and SOP-326 will be applied to assay standards
- d. PRO-837
- e. The report generated from the studies in PRO-837

5. We do not agree with your approach to temporarily allow forward processing of (b) (4) based on passing results of (b) (4) tests (identity by (b) (4)). We also note that you state you currently accept redundant identity tests both at the (b) (4) supplier and internally and will perform a validation of the supplier's CoA to eliminate the redundant internal identity tests and assess the appropriate

stage to complete the identity tests and update the documentation.

Additionally, we note based on SOP109 section 8.7.1 "Material testing may be performed concurrently with use in production under conditional release." We do not agree with routine conditional release for use of materials that you do not have results of QC tests required by the material specification sheets. Materials should only be released for use after the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality unit. This testing should include at a (b) (4) identity test which should be completed prior to the lot of material being released for use in manufacturing. Please confirm that you will update your procedures and SOPs to reflect that materials will be released for use after they have been sampled, tested and released by the quality unit.

Please submit the response in an Information Amendment to the submission through the Gateway by Monday, April 8, 2019. To expedite review, you may submit the responses directly to me (cc Wei Wang) via email in addition to submitting through the Gateway. Please confirm that you received this email, and contact me via phone or email with any questions or concerns regarding this submission.

Thank you-

Amanda

Amanda Trayer

Regulatory Project Manager

Center for Biologics Evaluation and Research

Office of Compliance and Biologics Quality

Division of Manufacturing and Product Quality

U.S. Food and Drug Administration

Tel: 240-402-7429

amanda.trayer@fda.hhs.gov