

From: Trayer, Amanda  
Sent: Wednesday, April 17, 2019 11:14 AM  
To: James L'Italien  
Cc: Wang, Wei (FDA); Robert Baker  
Subject: Teleconference and Information Request for BLA STN 125694/0

Importance: High

L'Italien-

Below is an Information Request in support of the review of BLA STN 125694/0. We would also like to schedule a teleconference to discuss this Information Request. Please let me know if your team is available tomorrow, April 18, 2019 at 1 PM EST or April 19, 2019 at 1 PM EST. Please provide a call in number for the call. I will be on leave starting this afternoon, so please copy Wei Wang on emails about the teleconference. I've included Robert Baker on this email since he was on the last teleconference with the DMPQ members of the review team.

Please address the following items:

1. Your SOP-532 (version 1.0) is inadequate. The following sections in the SOP-532 (version 1.0) are inconsistent with a statement in Section 3.2.S.2.2 of the original BLA submission, STN 125694/0, which indicates that there are no (b) (4) steps in the AVXS-101 Drug Substance Commercial Manufacturing Process:

"8.1.7 (b) (4) shall only be allowed for:

\* 8.1.7.1 (b) (4) operation for a batch within the (b) (4) manufacturing process.

\* 8.1.7.2 (b) (4) operation for a batch within the (b) (4) manufacturing process.

\* 8.1.7.3 (b) (4) operation for a batch within the drug product manufacturing process.

8.1.8 The cumulative impact of (b) (4) steps should be considered prior to a decision to perform a (b) (4) step in a subsequent unit operation. The acceptability of any (b) (4) batch shall be determined on a case-by-case basis and final disposition resides in the non-conformance report”.

In addition, you have listed (b) (4) required to achieve range criteria” as (b) (4) of the (b) (4) conditions for (b) (4) in revised Section 3.2.P.3.3. We consider this condition for (b) (4) unjustified because adequate control of the (b) (4) Step is an essential requirement for the commercial GMP manufacturing of the AVXS-101 Drug Product.

At this review time-point, the use of a (b) (4) (i.e. the Sterile Filtration (b) (4) step is (b) (4) of AVXS-101 DP) during the AVXS-101 Drug Product manufacturing process is limited by the following conditions:

- \* Failure of the (b) (4) sterile filter (b) (4) .
- \* Loss of integrity of the (b) (4) the filtered DP and the filling needle.
- \* Setup issues associated with the filling needle assembly not caused by operator error.

All other (b) (4) conditions would require a pre-approval supplement (PAS). Please acknowledge.

Please submit the response in an Information Amendment to the submission through the Gateway by Tuesday, April 23, 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 Information Request.

Thank you-

Amanda

Amanda Trayer

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