



FACSIMILE TRANSMISSION RECORD

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To: -----(b)(4)-----

From: Cherie Ward-Peralta, OBRR/CBER/FDA

Date: May 19, 2010

This Fax is regarding your submission, STN 125325/0 that was submitted to the Agency on May 29, 2009 as a biologics license application for Alpha-1 Proteinase Inhibitor (Human). In order to facilitate the review of the BLA, FDA requests the following additional information:

1. In your Process Validation Summary in Section 3.2.P.3.5, you state that -----(b)(4)----- does not affect the product quality and therefore -----(b)(4)----- Please elaborate on the circumstances represented by a -----(b)(4)----- Additionally, please provide a very detailed explanation of the procedure that you intend to use for ---(b)(4)--- of the product.
2. In Document RM-00017, Version 1, entitled *Risk Assessment for ---(b)(4)--- of the Maximum API Drug Product Formulation Lot Size from -----(b)(4)-----*, you state that the test equipment was -----(b)(4)----- prior to use (to simulate maximum potential SIP conditions during normal operations). Please explain whether you actually intend to SIP your -----(b)(4)----- If so, please explain what additional data you have to provide additional assurance that routine sterilization at this temperature will not adversely impact -----(b)(4)----- Additionally, please indicate the maximum temperature that the manufacturer of the -(b)(4)- recommends for -----(b)(4)-----.
3. In Appendix 1 of TR-Rep-VL-07704-PV/A2 entitled *Summary of the Alpha-1 Antitrypsin (AAT) Uniformity-of-Filling Validation*, you indicate that the results for the bulk formulated solution were greater than the difference specified for tests performed on duplicate samples. A decision was made to repeat the protein assay for this lot to determine with the differences in the test results represented real differences between samples as opposed to assay variability. Please indicate what your criteria are for repeat testing during validation studies. Further, please explain why there was assay variability in the first set of test results (which were atypical), whereas, there was less assay variability in the second set of test results (which were expected).

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Thank you.

Number of pages (including cover sheet) 3

4. In Summary Protocol Rep-VL-100332-PQ, entitled *Summary of Mixing Validation for Vessel T-55 for the AAT Product*, you indicate that the -----(b)(4)----- in ---(b)(4)-----, was different from the other sampling points, and presumably did not meet acceptance criteria. Instructions were given to improve the operating and sampling from the -----(b)(4)----. However, during the second run the -(b)(4)----- values still appear to be quite different than the other -(b)(4)- sampling points and do not meet acceptance criteria -----(b)(4)-----
- .
- Given these results, please indicate how you intend to address this lack of uniformity during this mixing step during the routine manufacturing process.
5. For the -(b)(4)- 15N filters, you indicate that filtration may occur through ---(b)(4)------. Please explain what actions will be taken -----(b)(4)-----
- .
6. Throughout the submission, there are a number of references to the process parameters for sterile filtration. However, not all of the process parameters are consistent. For example, in one instance the maximum sterile filtration pressure is -(b)(4)-, whereas in another instance this process parameter is listed as -(b)(4)-. Please provide limits for pressure, flow rate, and time based on your filter validation studies and the process validation studies.
7. Please provide maximum limits for different categories of defects that will be used in the 100% visual inspection process that are based on historical data generated from lots that have been already manufactured.
8. For the Comparability Protocol provided in Section 3.2.R.2, please provide the following information:
- Any operational parameters to be used for the -(b)(4)- process.
 - Elaboration on the cleaning studies that will be performed on the -(b)(4)- and submitted with the follow-up supplement.
 - A description of the specific types of testing that will be performed during the validation study (the proposal contains phrases such as "Test results for in-process quality attributes..." without referencing the specific tests).
 - The reporting category you intend to use for the supplement to be submitted to CBER that contains data generated from the executed Comparability Protocol.
9. Regarding the "package integrity test," or the container closure integrity test, performed on your product.
- Please describe:
 - Positive controls used in the test (including hole diameter).
 - Differential pressure(s) exerted on the vials during -(b)(4)- used to simulate processing or distribution conditions.
 - Limit of detection that the method can detect -----(b)(4)-----

- b. Please elaborate on how the (b)(4)-, as you have implemented it, correlates to microbial ingress.
- c. Lastly, please define a critical leak rate that is appropriate for your container closure system and provide sensitivity data demonstrating that your method can achieve this level of detection.

We would appreciate a response to this information request by June 2, 2010.

Please contact me if you have any questions.

Sincerely,

Cherie Ward-Peralta
Regulatory Project Manager
DBA/OBRR/CBER/FDA
Tel: (301) 827-9170