

From: Wood, Lorraine
Sent: Friday, May 12, 2017 3:07 PM
To: MaryAnn Lamb <MaryAnn.Lamb@bpl-us.com>
Subject: Information Request for BLA 125644/0 HAS: CMC
Importance: High

Dear Dr. Lamb,

We are reviewing your submission for BLA 125644 Human Albumin Solution (HAS) 5% and 25% and we request the following information to continue our review:

1. Section 3.2.S.2.2 provides an overview of the plasma pooling scheme. Please provide the details of this process to include reception of plasma into manufacturing site, storage, pooling vessel, containment of (b) (4) plasma, removal of (b) (4) plasma from container, control of starting material volume, calculation of yields, and testing for contamination, and hold times.
2. In section 3.2.S.2.the section designated as 2.4.1, determination of (b) (4) , there are several elements missing. Please provide the information listed below.
 - a) Please provide the results of sample testing and the raw data for performance qualification lots.
 - b) Please identify the samples used for testing including their identity and method of preparation
 - c) Please provide statistical calculation of error in measurement
3. Module 3.2.S.2.4, section 2.4.1 determination of (b) (4) requires the use of a standard for construction of a standard curve and system suitability. Please describe this standard, or provide an explanation for why no standard was used.
4. Section 3.2.S.2.2 refers to “(b) (4)” Please clarify the meaning of this term.
5. Section 3.2.S.2.4 describes results for the accuracy of the method for determination of (b) (4) concentration. Results of this testing show that the acceptance criterion for sample (b) (4) was not met. The reported percent recovery is only (b) (4) . The manufacturer’s explanation that this result is not significant, because sample (b) (4) that was analyzed with the same amount of spiked (b) (4) was showed a percent recovery within the acceptance criterion, is not acceptable. It appears based on information given in Table 11 that sample (b) (4) had an unspiked (b) (4) concentration of approximately (b) (4) and sample (b) (4) had an unspiked (b) (4) concentration of approximately (b) (4) . These are essentially two different samples and are not directly comparable. Please provide data for analysis of a

third sample with an unspiked (b) (4) concentration of (b) (4) and two additional samples with unspiked (b) (4) concentrations of (b) (4), respectively.

6. Please clarify Table 12 in section 3.2.S.2.4. that was provided for the repeatability studies.
 - a) What assay was used to generate these numbers?
 - b) How were these values calculated?
 - c) Please provide the original results used to generate these values
7. The data provided in Table 13 of section 2.4.2 of module 3.2.S.4 is inadequate. A detailed text should be provided describing the nature of the samples analyzed, and the method of analysis. In addition, testing of intermediate precision requires testing of within laboratory variability. Please indicate which variables were used to generate the results in Table 13.
8. Please provide explanations for a (b) (4) response for a (b) (4) concentration of (b) (4) in figure 4 of section 2.4.2 of module 3.2.S.4.
9. The data provided in table 15 of section 2.4.2 of module 3.2.S.4 only provides values for (b) (4). Were these the only concentrations tested?
 - a) What is the lower and upper limit of detection for this method?
 - b) What is the linear range of the method?
10. Please explain why batch (b) (4) 5% HAS is out of compliance for visual inspection and submit any out of specification reports and deviation investigations.
11. Please clarify whether the performance qualification lots were manufactured consecutively.
12. In section 2.4.1, determination of (b) (4), Please provide a clear statement of the assays ability to detect (b) (4) in the matrix used for sample analyses.
13. In section 3.2.P.5.1 specifications, please clarify the meaning of (b) (4) in terms of (b) (4).
14. Please note that the manufacturing process for plasma-derived product must be validated for its capacity to clear enveloped viruses, including HIV by at least two major and independent viral clearance steps. Each clearance step should provide > 4 logs of clearance, and the cumulative log reduction for a given virus should be > 10 logs. In your submission, HIV inactivation by heat treatment has been validated, however, no studies were performed to validate its removal by the (b) (4) steps. As a result, the level of HIV inactivation that you have reported (6.7 logs) is not sufficient, and must be supplemented by validating additional steps in the manufacturing process to clear HIV.

15. Section 3.2.S.2.3 section 1.2.1 describes some specifications for the (b) (4) . How is system suitability established for this (b) (4) ?
16. In section 3.2.S.2.4 there is a lack of detail in the background for the (b) (4) method validation. The exact type of (b) (4) must be defined. The nature of the (b) (4) system must be explicitly stated. The apparatus used for the analysis must be clearly described. The (b) (4) used for (b) (4) must be stated. The nature of the external standard must be described as well as its storage and qualification.
17. In section 3.2.S.2.4 Please provide the background on the nature and preparation of samples that were used to generate the data in Table 19. This should include calculation of concentration from the raw data, and a description of both positive and negative controls used for the assay. There are also an inadequate number of samples tested, a minimum of three determinations for three sample, or six determinations at 100% the sample concentration is required according to ICH Q2.
18. In section 3.2.S.2.4 the results of experiments for repeatability are given in Table 20. This section lacks details on the nature of the samples used and how the samples were prepared. There are also an inadequate number of samples. At least three samples should be used to generate the data. The criterion for acceptance also was not met. An acceptance criterion of an RSD of (b) (4) was established and the RSD of the samples tested were (b) (4) . The explanation that repeatability results were either at or close to the assay detection limit and that this represents a challenge to the LIMS system is not acceptable. The reliability assay should be repeated according to ICH Q2 (R1)
19. In section 3.2.S.2.4 table 21 the values given for the measurement of intermediate precision failed. The manufacturer's explanation for the failure was the same as the explanation for the failure of the repeatability measurements. The measurement of intermediate precision should be repeated, or the assay for determination of (b) (4) should be modified and revalidated.

Please respond to this request by May 26, 2017.

Thank you
Lorraine

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