



Our STN: BLA 125644/0

BLA COMPLETE RESPONSE

Bio Products Laboratory
Attention: MaryAnn Lamb PhD
Bio Products Laboratory USA, Inc.
302 East Pettigrew Street, Suite C-190
Durham, NC 27701

Dear Dr. Lamb:

This letter is in regard to your biologics license application (BLA) for Human Albumin 5% and 25% manufactured at your Elstree, Hertfordshire, United Kingdom location and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendments dated June 30, 2017 through August 17, 2017 as noted below. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CMC

1. Regarding the information provided for determination of accuracy for the (b) (4) testing method described in section 2.4.2 of module 3.2.S.4:

Results of this testing show that the acceptance criterion for sample (b) (4) was not met. The sponsor stated in their response received on May 26, 2017 (STN 125644/0.15) that there are no comparable samples currently available to provide the additional data. BPL commits to performing additional work when the manufacture of the product is scheduled and samples become available. Please note that the unspiked (b) (4) concentrations are dependent on the process for each batch, and as such (b) (4) concentrations of exactly (b) (4) cannot be guaranteed. Please provide proper validation data for this method prior to approval.

2. Regarding the evaluation of (b) (4) testing (in section 3.2.S.2.6) of the (b) (4) for production batches (b) (4), an expired (b) (4) was used for an (b) (4) assay for (b) (4) during the validation testing of the (b) (4) step. Please validate this assay using non-expired materials.
3. Regarding the information provided for viral clearance submitted on May 26, 2017 under STN 125644/0.15:

The information provided did not establish viral clearance for Human Immunodeficiency Virus (HIV) using at least two major and independent viral clearance steps where each clearance step provides > 4 logs of clearance. The cumulative log reduction for a given virus is recommended to be greater than 10 logs. In your submission, HIV inactivation by heat treatment has been validated; however, no studies were performed to validate HIV removal by the (b) (4) steps. BPL indicated that they can provide FDA with this confirmatory information no later than end Q2 2018. Please submit complete viral clearance data for the HIV virus.

4. Regarding the information provided on May 26, 2017 under Amendment STN 125644/0.15 (module 3.2.S.4) for (b) (4) concentration determination method:
 - a. The results of the repeatability studies for validation of (b) (4) determination failed according to the sponsor's own established standards. Please submit validation data to demonstrate repeatability of (b) (4) determination.
 - b. The results of the intermediate precision studies for validation of (b) (4) determination failed according to the sponsor's own established standards. Please submit data that demonstrates intermediate precision for (b) (4) concentration determination.
 - c. An inadequate number of samples was used in the accuracy studies for validation of (b) (4) concentration determination. The sponsor committed to provide new data with the appropriate number of samples no later than July 21, 2017. As of July 24, 2017, this data has not been received. Please provide the requested data included in the accuracy studies for validation of (b) (4) .
5. Regarding the validation of (b) (4) on linearity assessment, Table 29 (3.2.P.5.3 section 1.2.3.3 page 26), which was submitted on June 30, 2017 under Amendment STN 125644/0.22 in response to the information request question # 2, on May 5th, 2017:
 - a. This response was submitted beyond June 21 and is considered to be open to further review.
 - b. You stated that the information given in 3.2.P.5.2 section 1.3.3 page 10 on (b) (4) representation ((b) (4) assigned to (b) (4) respectively), is incorrect as it shows the calculation for Immunoglobulin products. Please provide an updated analytical procedure and validation report including the correct albumin calculation.
6. Regarding the validation of (b) (4) for the determination of aluminum (3.2.P.5.3 section 1.2.5.2), which was submitted

on June 30, 2017 under Amendment STN 125644/0.22 in response to the information request question # 7, on May 5th, 2017:

- a. This response was submitted beyond June 21 and is considered to be open to further review.
 - b. You stated that 25% Albumin ((b) (4)) was not used for the linearity test and that the range limit is incorrect for this assessment. It was also indicated in the submission that the intermediate precision assessment for batch (b) (4) did not meet the acceptance criteria. Please revalidate the method and provide the correct validation report.
7. Regarding the validation of analytical procedures for both (b) (4)
 - (Drug Substance, 3.2.S.4.3):
- Please provide a detailed description of the conditions used for the assessments of repeatability and intermediate precision that includes variations in days, analysts, and equipment. The method validation should also include accuracy, linearity and specificity assessments.
8. Regarding the validation of analytical procedure for determination of (b) (4)
 (3.2.P.5.3), please submit an updated validation report that includes linearity assessment.

FACILITY

9. Regarding the list of the equipment and processing rooms used in Steps (b) (4)
 , which was submitted on January 24, 2017 under Amendment STN 125644/0.1 in response to the information request question #4.a., dated on January 17, 2017:

You stated that (b) (4) Vessels are used for Step (b) (4)
 . You indicated in this list that these vessels are not used for the manufacture of other US licensed products. However, you did not provide a description for these vessels, nor did you provide the summary of the Performance Qualification and Cleaning Validation studies to support the manufacture of HAS 5% and 25%. Please provide a description for the (b) (4)
 Vessels and the latest summary reports for the Performance Qualification and Cleaning Validation studies. Please also include a summary of the testing conducted with results and acceptance criteria, and any deviations with their resolutions. In addition, please provide a summary of the cleaning procedure for the removal of prions with their respective acceptance criteria.

10. Regarding the list of the equipment and processing rooms in support for the manufacture of the Drug Product for HAS 5% and 25%, submitted on January 24, 2017 under Amendment STN 125644/o.1 in response to the January 17, 2017 information request question #5.b:

You did not provide a description for the (b) (4) Vessels, and you did not provide the summary of the Performance Qualification and Cleaning Validation studies for them to support the manufacture of HAS 5% and 25%. Please provide a description for the (b) (4) vessels used for the (b) (4) Vessels, and the latest summary reports of the qualification and Cleaning Validation studies. Please also include a summary of the testing conducted with results and acceptance criteria, and the deviations with their resolutions. In addition, please provide a summary of the cleaning procedure for the removal of prions with their respective acceptance criteria.

11. Regarding Part 1.1, in Section 2.3 from the original BLA STN 125644/o (received on December 09, 2016):

You provided a list of US licensed plasma derived products and other plasma derived products manufactured in your facility. However, it is unclear if the manufacture of these products is conducted on a campaign basis or concurrently. Please clarify.

12. Regarding the list of dedicated, shared and single-use equipment provided under Amendment STN 125644/o.6 (received on April 24, 2017):

- a. It was noted that several pieces of equipment are dedicated for the manufacture of Albumin. Please clarify if this equipment is used for the manufacture of Albumin for other markets. If so, please describe the controls in place to prevent contamination, cross-contamination and mix-ups, including but not limited to cleaning, removal of prions, containment, segregation, change-over and line clearance controls.

13. You stated in Section 3.2.S.2.2 of the original BLA STN 125644/o (received on

(b) (4)

(b) (4)

Government	Percentage
Current government	85%
Previous government	15%

Responsibility	Percentage
Current government	85%
Previous government	10%
No government	5%

Responsibility	Percentage
Current government	85%
Previous government	10%
Neither	5%

14. Regarding (b) (4) (Step (b) (4) – DP Manufacture Process) – Microbiological Lot Review from the batch records of Lots (b) (4) in Section 3.2.R from the original BLA STN 125644/o (received on December 09, 2016):
 - a. It was noted that you reported only the sterility and endotoxin release testing results as “Pass” on this form. It was noted in both batch records that bioburden in-process testing was conducted in several (b) (4) Drug Product manufacturing steps. Also, you conducted endotoxin testing and sterility testing during Drug Product manufacture. However, the results from this testing were not documented on this form. Please explain the reason for not documenting all bioburden, endotoxin and sterility testing results from the respective (b) (4) DP manufacturing steps. Please provide the results from the bioburden in-process testing, sterility and endotoxin release testing in support for Lots (b) (4) .
 - b. In addition, you conducted Environmental Monitoring (EM) during the filling step. Please explain the reason for not documenting the EM results from the filling step on this form. Please provide the EM results during the filling step for these lots
15. Regarding the summary reports PPQR /805/o/01/01 and PPQR/805/o/03/01 provided in Amendment STN 125644/o.3 (received on March 29, 2017):
 - a. It was noted that you did not provide the EM results in support for the filling of all the PPQ lots. Please provide the results in support for the filling of all PPQ lots. Please include the acceptance criteria and sampling locations.

- b. You did not provide the results in support for the filling, heat treatment and (b) (4) of sub-lots (b) (4) in the summary report PPQR/805/o/01/01. However, a summary of these results was provided in the summary for the PPQ study in the original application. Please provide an updated copy of this summary report, which includes the results in support for the filling, heat treatment and (b) (4) from these sub-lots.
 - c. The description of the deviations included in summary reports PPQR/805/o/01/01 and PPQR/805/o/03/01 is not clear. Please provide detailed narrative that describes these deviations, the root cause investigation, and the action(s) taken for their resolution.
 - d. It was noted in Section 3.2.P.3.5.1 from the original BLA (received on December 09, 2016) that bioburden in-process testing was conducted to (b) (4). However, the results of this in-process testing were not included in the summary reports PPQR/805/o/01/01 and PPQR/805/o/03/01. Please provide the bioburden testing results.
16. Regarding Sections 3.2.P.3.5.1, 3.2.P.7.1 and 3.2.P.8.3.1 from the original BLA STN 125644/o (received on December 09, 2016):

It was noted in the summary for the PPQ study from the original application that you used (b) (4) types of stoppers [(b) (4)] and overseals ((b) (4)). However, you did not specify the rationale for using these components in this study. In addition, you provided diagrams of these components in Section 3.2.P.7.1 in the original application, but it was noted that you did not provide a description of the similarities and differences for these components in this BLA. Also, it is unclear which type of stopper and aluminum overseal will be used during routine filling of HAS 5% and 25%.

- a. Please provide a table that lists the similarities and differences for these stoppers and overseals.
 - b. Please explain the rationale for using (b) (4) types of stoppers and overseals in the PPQ study in for HAS 5% and 25%. Also, please indicate which type of stopper and aluminum overseal will be used during routine filling of HAS 5% and 25%.
17. Regarding summary report PQR06800102, approved on November 2013 and provided in Amendment STN 125644/o.10 (received on April 28, 2017), it was noted that the content of this report is the same as that included in summary report PQR06800101, approved in January 2001. Therefore, it is unclear what additional testing was conducted and reported in this PQ study. Please

provide a complete description of the PQ testing, the results and acceptance criteria for PQR06800102.

18. Regarding summary report PQR/524/o/01/o provided in Amendment STN 125644/o.10 (received on April 28, 2017):

You indicated that a deviation was issued because the total protein reconciliation from (b) (4) for PPQ lot (b) (4) was below the lot processing limit. However, you did not provide the acceptance criterion for the total protein reconciliation from (b) (4), nor the total protein reconciliation from (b) (4) result for this lot. In addition, you did not provide a description of the action taken for this calculation in support for the manufacture of further lots for HAS 5% and 25%. Please provide the acceptance criterion for the total protein reconciliation from (b) (4) and the total protein reconciliation from (b) (4) result for PPQ lot (b) (4). In addition, please provide a description of the action taken for this calculation in support for the manufacture of further lots for HAS 5% and 25% in support for this deviation.

19. Regarding summary report PQR482/o/01/01 provided in Amendment STN 125644/o.10 (received on April 28, 2017):

- a. You stated that Deviation QR79676 was issued due to failure to measure the (b) (4) from the (b) (4) rinse at the (b) (4) cycles after the (b) (4) of lots (b) (4). You indicated that an investigation was initiated due to this issue and DP lots ((b) (4)) were placed on hold. However, you did not explain the actions taken to resolve this issue. Please provide a description of the actions taken to resolve this deviation and further issues with the (b) (4) reading (b) (4) cycle in this (b) (4) system.
- b. It is unclear if this PQ study was considered acceptable, since it did not comply with the (b) (4) acceptance criterion from the (b) (4) rinse at (b) (4) cycle. Please clarify if this study is considered acceptable or not. Also, clarify if an additional study has been conducted to evaluate the (b) (4) from the (b) (4) rinse (b) (4) cycle. If so; please provide a summary of this study with the results and acceptance criterion.

20. Regarding summary reports (b) (4) for the (b) (4) re-qualification of the Albumin Heat Treatment (b) (4) provided in Amendment STN 125644/o.10 (received on April 28, 2017):

- a. You did not provide a complete description of the re-qualification runs at 60°C in both reports. Please clarify whether these studies were conducted using a product load or a “simulated load” of product. Also indicate the

number of thermocouples used and their location in these studies. In addition, please clarify if you conducted any testing to determine the viral inactivation as part of these studies.

- b. You reported an incident associated with (b) (4) thermocouples that did not comply with the post-calibration criterion of (b) (4) . Please indicate the number of thermocouples required to pass this criterion and explain the reason to consider this PQ study as acceptable, since (b) (4) thermocouples did not pass the mentioned post-calibration error criterion.
 - c. You stated that Deviation QR93901 associated with the duration of “(b) (4)” stage did not comply with the criterion of (b) (4) and one of the probes ((b) (4)) of the (b) (4) did not comply with the criterion (b) (4) during (b) (4) stage. However, the action taken to resolve this deviation was not included in (b) (4) . Please explain the actions taken to resolve this deviation. Also, please explain the reason to consider this PQ study acceptable given the issues described in Deviation QR93901.
21. Regarding summary report PQR/773/o/o1/o1 provided in Amendment STN 125644/o.10 (received on April 28, 2017):
- You stated that Deviation QR83855 was due to a (b) (4) probe located in an empty (b) (4) that did not comply with the criterion of (b) (4) . Also, you indicated that this issue did not affect this study. Please clarify if this (b) (4) probe was used in this PQ study. Also, please explain the reason to consider this PQ study acceptable, since a (b) (4) probe did not comply with the criterion of (b) (4) .
22. Regarding the summary of the aseptic filling simulation program provided in Amendment STN 125644/o.3 (received on March 29, 2017):
- a. Please specify the number of aseptic filling simulation (AFS) runs performed every (b) (4) , and the number of runs performed in the case that there are changes in the aseptic filling of plasma derived products in the AFS.
 - b. Please clarify if EM is conducted as part of the aseptic filling simulation studies, and justify your response.
23. Regarding Section 3.2.P.3.5.2 from the original BLA (received on December 09, 2016):

You provided a description of the Container Closure Integrity Test (CCIT) for HAS 5% and 25% Drug Product. However, you did not provide the summary report of the CCIT in support for this BLA. Also, you did not indicate the

number of positive control vials used per CCIT run and how you prepared them.

- a. Please clarify if Container Closure Integrity Testing (CCIT) has been conducted to the container/closure system for HAS 5% and 25% using (b) (4) types of stoppers [(b) (4)]. Please provide the summary report for the validation of CCIT in support for this BLA.
- b. Please provide a description of the positive and negative control vials used for the validation of the CCIT. In addition, please describe the positive controls used in these studies.

24. Regarding Section 3.2.A.1 from the original BLA (received on December 09, 2016) and from Amendment STN 125644/0.5 (received on April 21, 2017):

You did not provide a complete description of the Water Monitoring Program, including sampling frequency, acceptance criteria, actions to be taken in the case of an excursion and a summary of the results from the Water Monitoring conducted in the last year. Please provide a summary that describes the Water Monitoring Program, including sampling frequency, acceptance criteria, and actions to be taken in the case of an excursion. Also, please provide a summary of the results from the Water Monitoring conducted in the last year.

25. Regarding summary report CVR/748/0/02/01 provided in Amendment STN 125644/0.5 (received on April 21, 2017), you stated that the (b) (4). However, you did not state the soiling and rinse solutions used in this study. Please indicate the soiling and rinse solutions used in this study.

26. It was noted that you did not provide a description of the sanitization and sterilization process for upstream and downstream equipment ((b) (4)) in support for HAS 5% and 25%. Please provide descriptions of the sterilization process for upstream and downstream equipment ((b) (4)) in support for HAS 5% and 25%. Please provide the summary report for the validation of the process including but not limited to the testing conducted, with acceptance criteria and results. In addition please describe the deviations and summary of temperature readings with their cumulative lethality rate and acceptance criterion.

27. Regarding summary reports (b) (4) provided in Amendment STN 125644/0.10 (received on April 28, 2017):

- a. You did not specify the sterilizer/autoclave used for the sterilization of 32mm Stoppers for HAS 5% and 25%. Please indicate which sterilizer/autoclave is used for the sterilization of 32mm Stoppers for HAS 5% and 25%.

- b. It was noted in the title of these reports that (b) (4) are washers/sterilizers. Therefore, it is unclear if these equipment are used for the washing and sterilization of stopper or only for the sterilization of stoppers. Please specify the specific functions of (b) (4) : washers or sterilizers.
- c. Please provide a complete description of the full load re-qualification runs for stoppers conducted in both studies including but not limited to the load size, the number of thermocouples used in these runs and their location in the load, the Biological Indicators used (spore count and D value used) and their location in the load, as well as the results and acceptance criteria. Also, provide a summary of temperature readings with their cumulative lethality rate and acceptance criterion.

Labeling

- 28. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

For PDUFA products, please submit your meeting request as described in our guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*, dated May 2009. This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>, and CBER's *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. This document is available on the internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>. Both documents may be requested from the Office of Communication, Outreach, and Development, at (240) 402-8020.

We acknowledge receipt of your amendments dated June 2, 2017 through August 17, 2017. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

You may cross reference applicable sections of the amendments dated June 30, 2017 through August 17, 2017, in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact Lorraine Wood, at (240) 402-8439 or lorraine.wood@hhs.fda.gov.

Sincerely yours,

Orieji C. Illoh, MD
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Division of Blood Components and Devices
Office of Blood Research and Review
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