



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

**To:** Administrative File BL STN 125644/0.30 (DATS# 716008) for Human Albumin Solution 5% and 25%

**From:** Priscilla M. Pastrana, Consumer Safety Officer, CBER/OCBQ/DMPQ/MRB2

**Through:** CDR Qiao Bobo, Ph.D., RAC, Branch Chief, CBER/OCBQ/DMPQ/MRB2

**CC:** Lorraine Wood, RPM, CBER/OBRR/RPMS  
Amanda Trayer, RPM, CBER/OCBQ/DMPQ/ARB

**Subject:** **Responses to Complete Response Review Memo** Bio Product Laboratory Ltd. (BPL) (US License #1811) - Biologics License Application (BLA) for the Manufacture of Human Albumin Solution 5% and 25% at Their Hertfordshire Facility in the United Kingdom

**ADD:** June 19, 2018

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### **RECOMMENDATION:**

All DMPQ CR review issues associated with this BLA have been adequately addressed. I recommend approval of the amendment to the BLA for Human Albumin Solution 5% and 25% submitted by Bio Product Laboratory Ltd. on December 18, 2017 under Amendment #125644/0.30 (DATS# 716008) pending product office approval.

### **SUMMARY:**

CBER received the response on December 18, 2017 under Amendment #125644/0.30 (DATS# 716008) to a Complete Response (CR) letter that was sent to BPL on August 25, 2017. This CR is associated with the BLA in support for the manufacture of Human Albumin Solution (HAS) 5% and 25% for Infusion at their Hertfordshire facility in the United Kingdom. This BLA was received by the agency on December 09, 2016 under STN 125644/0.0 (DATS# 650659). In addition, they responded on March 30, 2018 under Amendment #125644/0.32 (DATS# 729821) to an Information Request (IR) on March 13, 2018.

### **Background:**

CBER received a BLA from BPL on December 09, 2016 under STN 125644/0.0 (DATS# 650659) in support for the manufacture of Human Albumin Solution (HAS) 5% and 25% for Infusion. BPL stated that HAS 5% and 25% are a sterile liquid formulations in doses of 12.5g and 25g, which are administered via intravenous. They indicated that HAS 5% and 25% are used for the treatment of hypovolemia, ascites, burns, nephrotic syndrome, acute respiratory distress syndrome, cardiopulmonary bypass and liver cirrhosis.

The firm explained that the manufacture of HAS 5% and 25% was developed from the pre-existing Intravenous Albumin (Human) –Zenalb® 4.5% and 20%, which is a product licensed in the UK. They indicated that the proposed manufacture of HAS 5% and 25% as a re-formulation of Zenalb® 4.5% and 20% was discussed with FDA in a Type C meeting (Meeting ID CRMTS #9311; Application Type and Number: PS002352) on April 30, 2014. It was decided in this meeting that a dual stabilizer formulation is required with physiological sodium content and protein concentrations of (b) (4) to comply with the US market as defined in 21CFR 640.81 (f) and 21CFR 640.82 (a) and (d).

BPL indicated that HAS 5% and 25% Drug Substance (DS) is manufactured from human plasma supplied from US licensed collection facilities and purified using (b) (4)

After formulation and aseptic filling into vials, the Drug Product (DP) is exposed to terminal heat treatment at 60.0°C ±0.5°C for 10 (b) (4) hours. (b) (4)

(b) (4) the DP is visually inspected, labeled and packaged. They stated that HAS 5% and 25% DP has a shelf-life of 36 months when it is stored in its original packaging at a temperature of < 30°C.

BPL specified that HAS 5% and 25% are manufactured in the same facility (Building (b) (4)), where other US licensed plasma derived products are manufactured. They indicated that manufacturing steps in support for the (b) (4)

(b) (4) of the DS are conducted using the same manufacturing process rooms and equipment as for the manufacture of other US licensed plasma derived products. The firm explained that the DS manufacturing steps (b) (4); in addition to the DP manufacturing steps (b) (4) are conducted using the same manufacturing process rooms and equipment used for the manufacture of Zenalb® 4.5% and 20%. BPL stated that the filling of HAS 5% and 25% are conducted using the same rooms and equipment as for the manufacture of other US licensed plasma derived products and Zenalb® 4.5% and 20%. Therefore, the Chemistry, Manufacturing and Control (CMC) and Establishment Description Sections of this BLA in support for the DS manufacturing steps (b) (4) and all the DP manufacturing steps of HAS 5% and 25% were discussed in the review memo issued on June 30, 2017.

It was noted during the initial review of this application that the following information was not provided or appears incomplete:

- Table of Contents that outlines the sections of the application;
- Introduction Section that outlines the facility, manufacturing steps and equipment that are used for the manufacture of other US license products; in addition, to those manufacturing steps and equipment that are new and applicable to the manufacture of HAS 5% and 25%;
- Description of the water and Heating, Ventilating, Air Conditioning (HVAC) systems; including changes done in these systems in support for the manufacture of HAS 5% and 25%. In addition, to description of the Environmental and Water Monitoring Programs with their acceptance criteria and results. Also, copies from the summary reports of the Qualification studies done in these systems in support for the manufacture HAS 5% and 25%;

- Facility diagrams that illustrate the area classification and differential pressure of the rooms used for the manufacture of HAS 5% and 25%;
- Description of facility systems (for example, facility/alarm monitoring system), including changes done in these systems in support for the manufacture of HAS 5% and 25%. In addition, to summary reports of the Qualification studies done in these systems in support for the manufacture of HAS 5% and 25%.
- Description of the controls to prevent contamination, cross-contamination and mix-ups; including containment, segregation, change-over and line clearance controls; as well, in-process controls implemented in their facility for the manufacture of plasma derived products. In addition, the description of the cleaning and disinfection processes of the areas and equipment used for the manufacture of plasma derived products;
- List of rooms used for the manufacture and packaging of US licensed products and other markets. In addition, the description of the controls implemented for the manufacture of products using non-US plasma in shared areas and equipment approved for the manufacture of US licensed products;
- Description of the general equipment design used for the manufacture of plasma derived products. Also, the description of the existing and new equipment used for the manufacture and packaging processes for HAS 5% and 25%;
- List of dedicated, share and disposable (single-use) equipment used for the manufacture and packaging of US licensed products and for other markets;
- List of equipment that use automated systems;
- Description of the shipping process from the plasma collection sites to the manufacturing facility. Also, the description of the incoming procedure for the plasma and materials used for the manufacture of HAS 5% and 25%;
- Manufacturing and packaging flow chart that illustrates each manufacturing and packaging step. In addition, a list and copies of the procedures used for the manufacture and packaging of HAS 5% and 25%;
- Copies from the batch records of HAS 5% and 25% lots manufactured in support for this application;
- Description of the vial inspection, labeling and packaging processes for HAS 5% and 25%;
- Description of the aseptic filling simulation program in their facility for the manufacture of plasma derived products and copies from the summary reports of the aseptic filling simulation studies in support for the filling of HAS 5% and 25%;
- Copies from the summary reports of the Performance Qualification studies for the equipment used for washing, sterilization and depyrogenation of components in support for the manufacture of HAS 5% and 25%. Also, copies from the summary reports of the Performance Qualification studies for the process equipment used for the manufacture and packaging of HAS 5% and 25%;
- Copies from the summary reports of the Process Validation and Cleaning Validation studies in support for HAS 5% and 25%. In addition, to copy from the summary report of the Container Closure Integrity Test (CCIT) in support for HAS 5% and 25%.

A filing notification with deficiencies was sent to BPL on February 07, 2017, to address the above potential review issues in this BLA. A telecon was held on March 13, 2017, to discuss these issues with the firm. They agreed that the requested information in the filing notification

letter will be provided as amendments to the original application. BPL provided half of the information requested in this filing notification in the following amendments:

Amendment No	Date
STN 125644/0.3, DATS #669524	March 29, 2017
STN 125644/0.5, DATS #673978	April 21, 2017
STN 125644/0.6, DATS #674188	April 24, 2017
STN 125644/0.7, DATS #674189)	April 24, 2017
STN 125644/0.8, DATS #674349	April 25, 2017
STN 125644/0.9, DATS # 674676	April 26, 2017
STN 125644/0.10, DATS #675334	April 28, 2017

BPL responded on January 24, 2017 (Amendment STN 125644/0.1, DATS #657890) and May 05, 2017 (Amendment STN 125644/0.11, DATS #676376) to Information Requests (IR's) dated January 18, 2017 and April 26, 2017.

DMPQ recommended to CR this application based on the responses submitted by BPL to the filing letter with deficiencies for the following reasons:

- Approximately half of the information requested (IR's) in the filing letter with deficiencies were responded and half of those responses were found to be deficient;
- Approximately half of the IR's from the filing letter with deficiency still have not been responded to.

On August 25, 2017, a CR letter was issued to BPL, to address deficiencies in the CMC and Establishment Description Sections of this BLA.

The scope of this CR review memo is the evaluation of the firm's responses to the deficiencies addressed in the CR letter. Furthermore, to an Information Request (IR) submitted to BPL on March 13, 2018 to request additional clarification regarding temperature excursion during the (b) (4). The responses to this IR were received on March 29, 2018. Based in the review of BPL responses to the CR letter and the IR sent on March 13, 2017, it can be considered that the issues reviewed in this CR review memo were resolved and closed properly. Therefore, it is recommended the approval of the responses to this CR letter.

### **CR Review:**

This review is for the responses received on December 18, 2017 under Amendment #125644/0.30 (DATS# 716008) for the CR letter issue on August 25, 2017. The CR questions appear italicized and a summary of the firm response and reviewer commentary appear in regular text.

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 and the summary of the 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 qualification and Cleaning Validation studies. Ensure to include a summary of the testing conducted with results and acceptance criteria; any deviations with their resolutions; and the summary of the cleaning procedure for the removal of prions with the respective acceptance criteria.*

(b) (4)

[Redacted text block containing multiple lines of information]

(b) (4)



(b) (4)

**CBER Comments:** The firm response appears acceptable. Also summary reports CVR/338/0/03/01 and CVR/338/0/03/02 were reviewed and found acceptable. However additional clarification is required regarding the root cause and resolution for the temperature excursion during the (b) (4) in Vessel (b) (4). **See IR Question #1 – 03/13/2018 (Below).**

1. *Regarding your response to the CR Letter Item # 9 received on December 18, 2017;*

*You stated in Table No. 10 on page 22 that the (b) (4) of lot (b) (4) was aborted due to the minimum temperature criterion of (b) (4) being exceeded. (b) (4) However, it is unclear what the root cause and the resolution to prevent further temperature excursions during routine manufacturing. Please indicate the root cause for this incident and the resolution to prevent further temperature excursions during routine manufacturing.*

**Firm Response:** BPL stated that root cause for this incident is the (b) (4) in the temperature of the vessels used for the (b) (4). They explained that the action taken was to abort the (b) (4) when the temperature complied with the above criterion.

The firm indicated that this temperature excursion during the routine (b) (4). They stated that it is stated in their procedures and batch records for the manufacture of (b) (4).

**CBER Comments:** The firm's response is acceptable.

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 125644/0.1 in response to the January 17, 2017 information request question #5.b.*

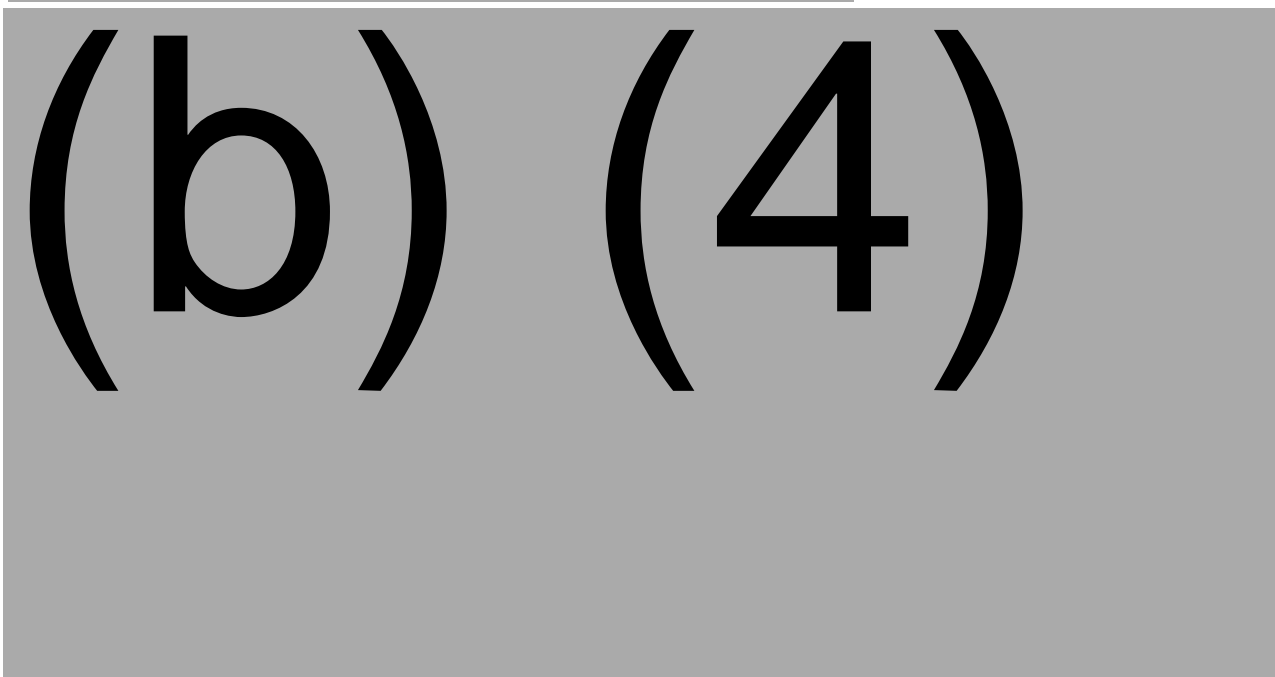
*You stated that (b) (4) Vessels are used for Drug Substance Steps (b) (4), Drug Product Steps (b) (4) are not used for the manufacture of other US licensed products. However, you did not provide a description for these vessels in the summary of the qualification and Cleaning Validation studies for them in support for 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. Ensure to 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.*

(b) (4)

The text "(b) (4)" is followed by a series of approximately 15 horizontal gray bars of varying lengths, representing redacted lines of text. These bars are arranged in two main groups: a first group of 8 bars and a second group of 7 bars, with a small gap between them.

(b) (4)

A large rectangular gray box covers the majority of the lower half of the page. The text "(b) (4)" is printed in large, bold, black font in the upper left corner of this box.





(b) (4)

(b) (4)

**CBER Comments:** The firm's response is acceptable. The summary reports associated to the PQ of the (b) (4) was reviewed and found acceptable.

11. *Regarding Part 1.1, in Section 2.3 from the original BLA STN 125644/0 (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 in a campaign basis or concurrently. Please clarify.*

**Firm Response:** BPL clarifies that the manufacture of the US licensed plasma derived products and other plasma derived products manufactured in your facility is conducted concurrently.

**CBER Comments:** The firm's response is acceptable.

12. *Regarding the list of dedicated, shared and single-use equipment provided under Amendment STN125644/0.6 (received on April 24, 2017):*

*It was noted that several 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 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.*

**Firm Response:** BPL clarified that the dedicated equipment used for HAS 5% and 25% DS and DP manufacturing processes are also used for the manufacturing of US licensed products and other markets. They indicated that US (b) (4) Plasma from US licensed centers is used for the manufacture of their products for US licensed products and other markets. The firm explained that the plasma donors are screened to ensure that they do not have human prion diseases such as vCJD or bovine BSE. BPL stated that the combined TSE removal from the purification process for Albumin of (b) (4). Therefore, the firm does not claim prion removal in support for the manufacturing process of US licensed products and for other markets.

The firm provided a description of the controls to prevent contamination, cross-contamination, and mix-ups in this response. This description consists in the cleaning, removal of prions,

containment, segregation, change-over and line clearance controls in support for the manufacture of HAS 5% and 25% and other US licensed products as follows:

- Use of US (b) (4) Plasma collected in US licensed centers is used for the manufacturing of their products for US licensed products and other markets;
- Segregation of manufacturing areas that allow the concurrently manufacturing of several products at the same time;
- HAS 5% and 25% DS and DP manufacturing process is an identical process as for other markets;
- Shared equipment used for the manufacturing of US licensed products and other markets;
- Product contact equipment made of stainless steel with seals and gaskets that comply with (b) (4) ;
- Line clearance, change over, cleaning and disinfection conducted in manufacturing areas at the end of the each DS and DP manufacturing step;
- Reconciliation of materials, DS and DP at the end of each manufacturing step;
- Fixed and portable vessels, fixed lines and other components (such as (b) (4) ) are cleaned using (b) (4) cycle;
- Small components are manually cleaned or cleaned in a part washer prior to be (b) (4) ;
- Labeling of equipment to identify their operational and cleaning status;
- Dedicated and segregated areas for the storage of cleaned and dirty equipment;
- Sterilization of product contact equipment and stoppers to be used in the filling process;
- Depyrogenation of vials to be used in the filling process;
- Aseptic techniques during the set-up of the filling line and filling process in the Aseptic Filling Suite (AFS);
- DP pass through a (b) (4) ;
- Environmental Monitoring (EM) conducted during filling process;
- Dedicated Air Handling Units (AHU's) in AFS;
- Materials has to disinfected prior to entered to the AFS;
- Cleaning and disinfection of AFS and filling line prior and after filling of each lot of DP;
- Heat treatment (b) (4) cleaned prior and post heat treatment of each lot of DP;
- DP segregated in cages and allocated spaces during (b) (4) ;
- Inspection and reconciliation of labeling and packaging materials prior and after operations;

**CBER Comments:** The firm's response is acceptable.

(b) (4)



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 125644/0 (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) (4)

(b) (4)

**CBER Comments:** The results from the bioburden in-process testing, sterility and endotoxin release testing in support for Lots (b) (4) were reviewed and found acceptable.

*b. In addition, you conducted Environmental Monitoring (EM) during the filling step. However, the results from these testing and the EM were not documented in this form. Please explain the reason to not documenting the EM results from the filling step on this form. Please provide the EM results during the filling step for these lots.*

**Firm Response:** BPL provided the EM results; in addition, to the sampling locations with their respective action limits in support for the filling of Lots (b) (4). They indicated that the sampling locations and action limit for the EM during filling processes are the following:

(b) (4)

BPL provided copy of QBT/00853/03/FRM, which describes the EM sampling locations in the filling room (b) (4), which are applicable to the filling of all the PPQ lots in support for this application.

The firm provided the EM results from Lots (b) (4). They indicated that all viable particulate count and personnel monitoring and non-viable particulate count results from these lots did not exceed the above action limit.

**CBER Comments:** The EM results from the filling of Lots (b) (4) in support for this BLA were reviewed and found acceptable.

15. Regarding the summary reports PPQR /805/0/01/01 and PPQR/805/0/03/01 provided in Amendment STN 125644/0.3 (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. Ensure to include the acceptance criteria and sampling locations.

**Firm Response:** BPL provided the EM results; in addition, to the sampling locations with their respective action limits in support for the filling of all the PPQ lots in support for this BLA.

The firm indicated that the sampling locations and action limit for the EM during filling processes are the following:

(b) (4)

BPL provided copy of QBT/00853/03/FRM, which describes the EM sampling locations in the filling room (b) (4), which are applicable to the filling of filling of all the PPQ lots in support for this application.

The firm provided the EM results from the filling of (b) (4) PPQ lots (Lots No. (b) (4)

(b) (4) ) in support for this BLA. They indicated that all viable particulate count and personnel monitoring and most of the non-viable particulate count results from these lots did not exceed the above action limit.

BPL explained that there was an excursion in one non-viable particle count sample from Lot No. (b) (4) and Deviation QR96540 was initiated to address this issue. They stated that the non-viable particulate count at (b) (4) in the (b) (4) (Class (b) (4)/ISO<sub>8</sub>) during (b) (4) change was (b) (4) and it exceeded the Action Limit of (b) (4). The firm explained that the root cause for this issue was the manipulation of the (b) (4) during changing the (b) (4). They indicated that filling process was not conducted during the (b) (4); therefore, the product in the filling line was not affected.

**CBER Comments:** QBT/00853/03/FRM and the EM results from the filling of Lots No.

(b) (4)

in support for this BLA were reviewed and found acceptable.

- b. *You did not provide a description of the results in support for the filling, heat treatment and (b) (4) of sub-lots (b) (4) in the summary report PPQR/805/0/01/01. However, a summary of these results was provided in the summary for the PPQ study from 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.*

**Firm Response:** BPL indicated that the results in support for the filling, heat treatment and (b) (4) of sub-lots (b) (4) was included in the summary report PPQR/805/0/01/02. This report was approved on June 2017 and it superseded summary report PPQR/805/0/01/01.

**CBER Comments:** The results in support for the filling, heat treatment and (b) (4) of sub-lots (b) (4) included in the summary report PPQR/805/0/01/02 were reviewed and found acceptable.

- c. *It is unclear the summary of all the deviations included in summary reports PPQR/805/0/01/01 and PPQR/805/0/03/01. Please provide a narrative that describes these deviations, the root cause investigation, and the action(s) taken for their resolution.*

**Firm Response:** BPL provided a table which summarized all the deviations, with their root cause investigation and actions taken in PPQR/805/0/01/01 and PPQR/805/0/03/01 as follows:

(b) (4)



(b) (4)

**CBER Comments:** The summary of the deviations with their root cause investigation and actions taken in PPQR/805/0/01/01 and PPQR/805/0/03/01 were found acceptable.

- 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 these in-process testing were not included in the summary reports PPQR/805/0/01/01 and PPQR/805/0/03/01. Please indicate the reason to not include these bioburden testing results in the summary reports PPQR/805/0/01/01 and PPQR/805/0/03/01. Please provide the bioburden testing results in support for these summary reports.*

(b) (4)

(b) (4)



(b) (4)

**CBER Comments:** The bioburden in-process testing results from the summary reports PPQR/805/0/01/01 and PPQR/805/0/03/01 were reviewed and found acceptable.

*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 125644/0 (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 ( ). However, you did not specify the reason to use these components in this study. In addition, you provided diagrams of these components in Section 3.2.P.7.1. from the original application. 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 enumerates the similarities and differences for these stoppers and overseals.*

**Firm Response:** BPL provided a table that enumerates the similarities and differences for these stoppers and overseals as follows:

(b) (4)

(b) (4)

**CBER Comments:** The firm's response is acceptable.

- b. Please explain the reason to use (b) (4) type 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%.*

**Firm Response:** BPL clarified that it was decided to use (b) (4)

They firm stated that (b) (4) stopper/overseal combinations will be used in routine filling of HAS 5% and 25%.

**CBER Comments:** The firm's response is acceptable.

- 17. Regarding summary report PQR068001.02, approved on November 2013 and provided in Amendment STN 125644/0.10 (received on April 28, 2017). It was noted that the content of this report is the same as included in summary report PQR068001 01, approved in January 2001. Therefore, it is unclear what the testing conducted in this PQ study covered. Please provide a complete description the PQ testing with acceptance criteria for PQR068001.02.*

**Firm Response:** BPL clarified that PQR068001.02 is a review of the original PQ study for the (b) (4). It consisted in the evaluation of deviations and change controls issued to this equipment after the completion of the original PQ study to corroborate if there is any change in the validated state and its operational parameters. The firm concluded in this PQ report that the (b) (4) maintained its validated state and there are no changes in the operational parameters.

**CBER Comments:** The firm's response is acceptable.

- 18. Regarding summary report PQR/524/0/01/0 provided in Amendment STN 125644/0.10 (received on April 28, 2017). You indicated that a deviation was issued due to 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) and 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, 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.*

**Firm Response:** BPL stated that the acceptance criterion for the total protein reconciliation from (b) (4) for HAS 25% and (b) (4) for HAS 5%. They indicated that the total protein reconciliation results from (b) (4) for HAS 25% and (b) (4) for HAS 5%.

Therefore, these results do not comply with the above limits and a deviation was issued. The firm explained that no action was taken

The firm explained that no action was taken for this calculation in support for the manufacture of further lots for HAS 5% and 25% for this deviation. They explained that the cause of the (b) (4) total protein recovery in lot (b) (4) of HAS 5% and 25% and collection of additional sampling for characterization testing in support for this BLA. BPL specified that (b) (4) lots is not conducted during routine manufacturing.

**CBER Comments:** The firm's response is acceptable.

19. Regarding summary report PQR482/0/01/01 provided in Amendment STN 125644/0.10 (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 (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 at (b) (4) cycle in this (b) (4) system.

**Firm Response:** BPL explained that the root cause for Deviation QR79676 was due to the (b) (4) was not monitoring the (b) (4) at the (b) (4) rinse of the (b) (4) cycle due to a software configuration error. They indicated that the manufacturer of the (b) (4) corrected this issue in June 2014. The firm indicated that (b) (4) testing was conducted to samples from the (b) (4) rinse of the (b) (4) cycle for these lots. They stated that these samples complied with a criterion of (b) (4).

**CBER Comments:** The firm's response is acceptable.

- 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 (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.

**Firm Response:** BPL decided to invalidate PQ study PQ482/0/01/01. They decided to repeat this study between July and August 2014 under PQ Protocol PQ482/0/01/03. Copy of the summary report PQR482/0/02/01 approved on September 2014 in support of PQ482/0/01/03 was provided in the responses to the CR Letter. The firm indicated that (b) (4) cycles were conducted in this (b) (4) System after the (b) (4) lots for Zenalb 20% (BDS Lots No. (b) (4)). BPL stated that these lots complied with most of the following testing criteria:

(b) (4)

The firm stated that three deviations were initiated in this study. Deviation QR 82185 was associated to the (b) (4) did not occur due to an input error. They indicated that the (b) (4) was conducted manually. BPL explained that manufacturer of this (b) (4) System fixed this input at the completion of this study and prior to initiate routine manufacturing. The firm corroborated that the (b) (4) occurred during routine manufacturing. Therefore, this deviation was resolved and closed.

Deviation 82340 was associated with a bioburden excursion in the (b) (4) due mishandling during (b) (4) this sample. They stated that the other bioburden (b) (4) samples collected in the (b) (4) System complied with a criterion of (b) (4). Deviation QR82821 was associated with a bioburden (b) (4) sample not collected. BPL indicated that the corrective action for both deviations was the retraining of the QC laboratory personnel in the bioburden sampling procedure.

**CBER Comments:** The firm's response is acceptable.

20. *Regarding summary reports (b) (4) for the (b) (4) re-qualification of the Albumin Heat Treatment (b) (4) provided in Amendment STN 125644/0.10 (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.*

**Firm Response:** BPL stated that the (b) (4) requalification of the Albumin Heat Treatment (b) (4) described in (b) (4) are conducted according to SOP TEC/00265, "Routine Re-qualification of the (b) (4) Pasteurisation Cycle," approved on March 2016. They explained that the load used in these studies consisted of (b) (4), in which (b) (4) as follows:

(b) (4)

SOP TEC/00265 provides diagrams that illustrate the location of the TC's in each (b) (4). They indicated that each TC is placed (b) (4) on the pre-determined location according to this SOP.

BPL clarified that viral inactivation were not conducted as part of the re-qualification studies conducted to the heat treatment (b) (4). They indicated that viral inactivation studies are conducted separately.

**CBER Comments:** The firm's response is acceptable.

- b. *You reported an incident associated with (b) (4) thermocouples that did not comply with the post-calibration error 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 the post- calibration error criterion.*

**Firm Response:** BPL specified in Section 7.11 from SOP TEC/00265 that all TC's used in this re-qualification study must not deviate more (b) (4) from the temperature reference reading during post-calibration. Also, this section stated that a risk assessment is conducted in the case that any TC failed post-calibration.

The firm stated that (b) (4) TC's failed the post use calibration criterion. They indicated that these TC's were placed in different locations in the load. BPL explained that an assessment was conducted, in which included the evaluation of the temperature recorded in (b) (4). They indicated that all TC's complied with a temperature range of (b) (4) for 10 hours (b) (4) hours during heat treatment step and no deviation was observed in the heat treatment process. The firm indicated that the temperature data from the other (b) (4) TC's are representative from the (b) (4) used in this study. They concluded that this incident did not affect (b) (4) and it was considered as acceptable.

**CBER Comments:** The firm's response is acceptable.

- 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 as acceptable given the issues described in Deviation QR9.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**CBER Comments:** The firm's response is acceptable.

21. *Regarding summary report PQR/773/0/01/01 provided in Amendment STN 125644/0.10 (received on April 28, 2017).*

*You stated that Deviation QR83855 was due to a (b) (4) probes located in an empty (b) (4) that did not comply with the criterion of (b) (4). Also you indicated that 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 as acceptable, since a (b) (4) probes did not comply with the criterion of (b) (4).*

**Firm Response:** BPL clarified that (b) (4) probe ((b) (4)) was damaged and provided erratic readings. This probe was located in an empty (b) (4). They stated that the probe was replaced and calibrated after this PQ study. The firm explained that dataloggers were placed near-by each (b) (4) probe during the PQ study of (b) (4) Room (b) (4). BPL explained, that this study is considered acceptable, since temperature recorded in the dataloggers complied with the criterion of (b) (4), as well, the temperature from the (b) (4) probes, with the exception of the damaged probe. The data from the damaged probe was considered as invalid.

**CBER Comments:** The firm's response is acceptable.

22. *Regarding the summary of the aseptic filling simulation program provided in Amendment STN 125644/0.3 (received on March 29, 2017).*

*It was noted that you did not specify the number of aseptic filling simulation runs done every (b) (4) and the actions to be taken in the case that there were changes in the aseptic filling of plasma derived products, such as introduction of new products to be filled in the Aseptic Filling Suite (AFS), major changes and maintenance (e.g. shutdown) in the AFS and filling line. Also, you did not state if EM is conducted as part of the aseptic filling simulation studies.*



- a. Please specify the number of aseptic filling simulation runs done 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.

**Firm Response:** BPL specified that one aseptic filling simulation run is done every (b) (4). They indicated that three aseptic filling simulation runs are conducted in the case of changes in the aseptic filling of plasma-derived products and after periods of shutdown of more than (b) (4).

**CBER Comments:** The firm's response is acceptable.

- b. Please corroborate if EM is conducted as part of the aseptic filling simulation studies.

**Firm Response:** BPL indicated that EM is conducted during aseptic filling simulations. This EM is the same as conducted during routine manufacturing.

**CBER Comments:** The firm's response is acceptable.

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 controls vials used per CCIT run and how you prepare them.*

- a. Please provide a copy for the summary report of the CCIT in support for this BLA.

**Firm Response:** BPL provided copies for the summary reports and protocols of the CCIT in support for this BLA as follows:

- CCIR/732/0/02/01 – CCIT Report for the New Filling Line (b) (4) Filling Units 100mL and 250mL L, approved on May 2015;
- CCIR/732/0/01/02 – CCIT Report for the New Filling Line (b) (4) Filling Units 100mL and 250m, approved on August 2016;
- CCI/910/0/01/01 – CCIT Protocol for (b) (4) Glass Bottle with New Stopper and Overseals : (b) (4), 32MM Stoppers and (b) (4), 32mm Overseals Crimped Using Line (b) (4), approved on March 2017.
- MET:195/116; 118-120 and MET:331/227-229, CCIT Report in Support for CCI/910/0/01/01, approved on May and July 2017.

The firm indicated that CCIR/732/0/02/01 and CCIR/732/0/01/02 are in support for the stopper (b) (4) and overseal part number (b) (4). They explained that these studies were conducted using (b) (4) test method to corroborate that there are no changes in the stoppering and crimping steps in the (b) (4) after the implementation of the new filling line ((b) (4)) in AFS. BPL stated that both CCIT were conducted in an external laboratory. They indicated that (b) (4) vials of 100mL and 250mL were respectively tested in CCIR/732/0/02/01. Also, (b) (4) vials of 50mL and 500mL were respectively tested in CCIR/732/0/01/02.

(b) (4)



(b) (4)

**CBER Comments:** The copies for the summary reports and protocols of the CCIT in support for this BLA were reviewed and found acceptable. However, it is unclear when the new filling line (b) (4) was approved for the manufacture of US licensed products. **See IR Question #2 – 03/13/2018 (Below).**

2. *Regarding your response to the CR Letter Item # 23.a. received on December 18, 2017;*

*You stated in Section 1.0 from CCIR/732/0/02/01 and CCIR/732/0/01/02, that Container Closure Integrity Testing (CCIT) was conducted to corroborate that there are no changes in the stoppering and crimping steps after the implementation of the new filling line (b) (4). Also, you indicated in these reports that this line is used for the manufacture of US licensed products. However, it is unclear when this line was approved for this purpose. Please provide the STN with approval date in support for the filling of US licensed products in the filling line (b) (4).*

**Firm Response:** BPL indicated that filling line (b) (4) was approved on October 2015 under STN 125329/115 for Immune Globulin Intravenous (Human), 5% Liquid.

**CBER Comments:** The firm's response is acceptable.

*b. Please provide a description of the positive and negative control vials used in the CCIT. In addition, please clarify if the stoppers of the positive control vials are (b) (4) in the hole made in these stoppers to simulate the (b) (4) hole in the stoppers.*

**Firm Response:** BPL explained that two positive and two negative controls were used in the CCIT. They indicated that the positive controls were prepared by (b) (4). These positive controls were exposed to the (b) (4) as the tested vials. The firm stated that the negative controls were not exposed to the (b) (4).

**CBER Comments:** The firm's response is acceptable.

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.*

**Firm Response:** BPL stated that bioburden and endotoxin sampling is conducted in their Water Monitoring Program. They provided the sampling frequency and action limit for bioburden and endotoxin as follows:

(b) (4)

The firm indicated that the action and alert levels are based on the historical data and they are evaluated on an annual basis. They explained in the case of an action limit excursion, an investigation is initiated and include an evaluation of how the process is affected and the sampling trending. If it is a bioburden excursion, the organism is identified. Then corrective and preventive actions are implemented to resolve the excursion and additional testing in the impacted sampling point. BPL stated that the investigation is close when the testing conducted to the sampling point does not exceed the action limit.

BPL provided a summary of the results from the Water Monitoring conducted in the last year. They indicated that no samples from the Purified Water Distribution System exceeded the action level and one bioburden excursion in the Purified Water Generation System. The firm stated ten bioburden excursions and 46 endotoxin excursions in the WFI system. BPL indicated that the bioburden excursions in the Purified Water Generation System and WFI system were associated to mishandling of samplings and the personnel in charge for sampling the Purified Water and WFI system were retrained. They explained that the endotoxin excursions were associated to inadequate sanitization in two manufacturing areas. Additional sampling was conducted after these areas were sanitized and they did not exceed the action limit. BPL stated that these excursions were resolved and closed.

**CBER Comments:** The firm's response is acceptable.

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)*

*(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.*

**Firm Response:** BPL stated that (b) (4) was used as soiling solution for this cleaning validation study. (b) (4) and it

was selected as the worst-case soiling solution according to the Report LR159409, “Product Removal – Worst Case Determination, Including Intermediate Samples.”

The firm indicated that the rinse solution used in this study consisted of (b) (4) for pre-rinse and final rinse steps. They stated that (b) (4) detergent were used in this study as cleaning agents. These solutions were used in this study according to the qualified cleaning procedure, PDN/00735.

**CBER Comments:** The firm’s response is acceptable.

26. *It was noted that you did not provide a description of the sanitization and sterilization process for upstream and downstream equipment ( ) in support for HAS 5% and 25%; in addition, to the summary report for this process. Please provide description of the sterilization process for upstream and downstream equipment ( ) in support for HAS 5% and 25%; in addition, to the summary report for this process. Ensure to include, but not limited to the testing conducted with acceptance criteria and results. In addition, to deviations, a summary of temperature readings with their accumulate lethality rate and accumulated lethality rate criterion.*

(b) (4)

(b) (4)

(b) (4)



(b) (4)

(b) (4)

**CBER Comments:** The firm's response is acceptable.

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%.*

**Firm Response:** BPL indicated that (b) (4) are used for the sterilization of 32mm Stoppers for HAS 5% and 25%.

**CBER Comments:** The firm's response is acceptable.

- 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 what the specific functions of (b) (4) : washers or sterilizers.*

**Firm Response:** BPL specified that (b) (4) have the functionality of washer/sterilizer. However, the washing function is not used for the stoppers in support for the manufacture of HAS 5% and 25%.

**CBER Comments:** The firm's response is acceptable.

- c. *You did not provide a description of the full load re-qualification runs for Stoppers in both studies. Please provide a complete description of the full load re-qualification runs for Stoppers conducted in both studies. Ensure to include, but not limited to the amount of each stopper size, the number of thermocouples used in these runs and their location in the load; in addition, the type of Biological Indicators with spore count and D value used in these runs, their location in the load, results and acceptance criteria. Also, please provide a summary of temperature readings with their accumulate lethality rate and accumulated lethality rate criterion.*

**Firm Response:** BPL provided a description of the full load re-qualification runs for Stoppers conducted in both studies. They indicated that one requalification run was conducted in each washer/sterilizer. The firm explained that each run consisted of (b) (4) 32mm stoppers, which is the amount of stoppers sterilized during routine manufacturing. BPL indicated that thermocouples (TC's) were placed in the following locations of each washer/sterilizer:

