

Our Reference: BLA 125644/0

Date: June 12, 2017.

Bio Products Laboratory Inc.

ATTENTION: Dr. MaryAnn Lamb

302 East Pettigrew Street, Suite C-190
Durham, NC 27701

Dear Dr. Lamb:

Attached is a copy of the agenda for your June 14, 2017 Mid-Cycle Communication Teleconference with CBER.

Please include a reference to Submission BLA 125644 in your future submissions related to the subject product.

If you have any questions, please contact me at (240) 402-8439 or lorraine.wood@fda.hhs.gov.

Sincerely,

Lorraine Wood, MS, MLS (ASCP)^{CM}
Regulatory Project Manager
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Agenda

Application type and number: BLA 125644/0

Product name: Human Albumin Solution (HAS) 5% and 25%

Proposed Indication: Hypovolemia, Ascites, Burns, Nephrotic syndrome, Acute Respiratory Distress Syndrome (ARDS), Cardiopulmonary bypass.

Applicant: Bio Products Laboratory

Meeting date & time: June 14, 2017, 11:00 am to 12:00 pm EDT

Committee Chair: Wayne Hicks, PhD

RPM: Lorraine Wood, MS, MLS (ASCP)^{CM}

Agenda:

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the review committee to date.

CMC

- 1) The failure on the part of the manufacturer to properly validate viral reduction for enveloped viruses
- 2) There are also several methods for in-process controls and product specifications that have not been properly validated.
- 3) BPL does not provide raw data, figures, or plots to accompany the summary tables for the drug substance characterization section. A complete description with raw data and figures (for all sections) is necessary for the reviewer to make a decision on the completeness of the submission. BPL should also provide SOPs for each assay used for drug substance characterization.
- 4) BPL did provide some of the information that should be provided for impurities (as listed in the Guidance for Industry). These include:
 - i. Identity of the impurity
 - ii. Analytical procedure used to detect or search for the impurity or potential impurity.
 - iii. An indication as to whether a potential impurity was actually detected in significant quantities in the drug substance

- iv. Structural characterization data and/or other data on the physical or chemical properties of the impurity.
 - v. A table listing the qualified level of expected impurities with a cross-reference to the appropriate studies.
 - vi. Data showing removal of impurity.
 - b. BPL however, did not provide SOPs, raw data or figures for the assays used to identify and show removal of impurities.
 - 5) As stated in the Guidance for Industry, all drug substance specifications should be listed with associated acceptance criteria. A detailed description, validation of the analytical test and justification for the specification and acceptance criteria should also be included. BPL did not provide SOPs, raw data or figures for the analytical methods nor did they provide justifications of specifications.
 - 6) Stability testing for drug product should be performed on the proposed in-use period (BPL proposes a shelf-life of 36 months for HAS 5% and 25%) on batches as part of the formal stability studies at initial and final time points, and if full shelf life, long term data is not available before submission, a minimum of 12 months on at least three conformance batches should be included in the submission. BPL. BPL only provides 3 months on production scale batches as of today. BPL did submit 12 months of pilot scale batch stability data for both concentrations. BPL will therefore need to provide updated stability data for all manufacturing scale and pilots batches for both 5% and 25% HAS.
 - 7) BPL needs to provide information on in house standards including procedures for the preparation, information on stability of standards and storage conditions, calibration standards, and system suitability standards.
 - 8) BPL needs to provide system suitability of all (b) (4) systems. These tests are used to verify that the (b) (4) system is adequate for the intended analysis. FDA recommends System Suitability testing parameters, (b) (4) for acceptance, release, stability, or impurities/degradation methods using external or internal standards.
 - 9) Analytical procedures are not described in sufficient detail as per the Guidance for Industry (“Analytical Procedures and Methods Validation for Drugs and Biologics”).
2. Information regarding major safety concerns. There are no major safety concerns at this time.

3. Preliminary review committee thinking regarding risk management.
The current thinking of the review committee is that a Risk Evaluation and Mitigation Strategy (REMS) not required.
4. Any information requests sent and responses not received

CMC: Questions: Submitted of March 6, 2017

- 1) Was the equipment used for (b) (4) manufacture previously used to manufacture of Albumin lots?
- 2) Please submit validation data for all equipment used to include heat pasteurization, filling apparatus (b) (4) ?
- 3) Please describe the location of all manufacturing equipment and manufacturing steps for (b) (4) that are part of the manufacturing process as a manufacturing flow diagram, or as a series of diagrams.
- 4) Please submit a table, or manufacturing flow diagram that outlines each manufacturing step, the equipment associated with each step and its location in the manufacturing site.
- 5) Please submit a table showing all in-process controls associated and the manufacturing step with which it is associated.
- 6) Please submit complete batch records for all conformance lots.
- 7) Please submit a report listing all deviations and out of specification results that occurred during validation studies for (b) (4) 5% and 25%.

Questions submitted as of May 12, 2017:

- 8) 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.
- 9) In module 3.2.S.2.4 section 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

10) 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.

11) Section 3.2.S.2.2 refers to “(b) (4)” Please clarify the meaning of this term>

12. 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 the manufacturing site, storage of plasma, pooling vessel(s), containment of (b) (4) plasma, removal of (b) (4) plasma from container, control of starting material volume, calculation of yields, testing for contamination and yields.

13) Section 2.42 of module 3.2.S.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) showed a percent recovery that was 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 0% and two additional samples with unspiked (b) (4) concentrations of (b) (4) respectively.

14) Please clarify Table 12 which 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

15) 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.

- a) Testing of intermediate precision requires testing of within laboratory variability. Please indicate which variables were used to generate the results in table 13.

16) Why is there 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/

17) 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?

18) 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?

19) Please clarify whether the performance qualification lots were manufactured consecutively.

20) 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.

21) In module 3.2.P.5.1 specifications, please clarify the meaning of (b) (4) in terms of (b) (4)

22) “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.

23) Module 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)?

24) In module 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.

25) In module 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.

26) In module 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)

28) In module 3.2.S.2.4 table 21 the values given for the measurement of intermediate precision also 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.

29) Is the final product Pasteurized using a water bath, or is another type of heating used?

Additional Outsanding Information Request

- 1) Section 3.2.S.3.1 ((b) (4) and other characteristics):
- 2) Please provide all raw data including (b) (4) used to determine (b) (4) of drug substance.
- 3) Please provide a detailed description of how (b) (4) performs (b) (4) for determining (b) (4)
- 4) Section 3.2.S.3.2 (Impurities)
- 5) Please provide raw data including figures representing (b) (4) for the (b) (4) step used to remove impurities.
- 6) Please provide raw data for the (b) (4) assay for each impurity. Include standard curve data used to quantify each impurity.

7) Section 3.2.S.4 (Specifications)

8) Please provide a detailed justification for specifications related to (b) (4) (Table 1).

9) Please provide raw data and figures for batch Process QC results listed Tables 3 and 6.

10) Section 3.2.S.7 (Stability Summary and Conclusions):

- a. The stability summary and conclusions are incomplete. Only 5% HAS drug substance stability data (representing (b) (4)) has been submitted for (b) (4) time intervals up to (b) (4) . Long-term stability studies should be performed for both 5% and 25% HAS under normal and accelerated storage conditions. If available, please provide long-term stability data for both 5% and 25% HAS drug substance with parameters, temperature conditions, and time points in accordance with ICH guidelines.

11) Section 3.2.P.8 (Product stability Data)

12) Limited stability is available on HAS 5% and HAS 25% final products. Please provide updated drug product stability data for all manufacturing scale and pilots batches for both 5% and 25% HAS.

13) In order to review the BPL established arrangement for sampling and testing; please provide stability protocols SSP/00141 (manufacturing scale batches) and SSP/00138 (pilot scale batches).

14) Requested the procedures and validation data of the NAT tests performed by each of the outside contractors that performed QC testing for NAT testing of plasma pool.

Facilities:

15) 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/o.1 (DATS #657890) in response to the information request question #4.a., dated on January 17, 2017.

- a. 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; in addition, to 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 and copies from their latest summary reports of the qualification and Cleaning Validation studies. Ensure to

include a summary of the testing conducted with results and acceptance criteria; in addition, to deviations with their resolutions. In addition, please provide a summary of the cleaning procedure for the removal of prions with the respective acceptance criteria.

16) Regarding the list of the equipment and processing rooms in support for the manufacture of the Drug Product for HAS 5% and 25%, which was submitted on January 24, 2017 under Amendment STN 125644/O.1 (DATS #657890) in response to the information request question #5.b., dated on January 17, 2017.

a. You stated that (b) (4)

(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)

(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.

17) Regarding Part 1.1, in Section 2.3.

a. 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.

18) Regarding the list of dedicated, shared and single-use equipment provided in Amendment STN 125644/O.6 (DATS #674188).

19) 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; not limited to cleaning, removal of prions, containment, segregation, change-over and line clearance controls.

20) It was noted that shared equipment will be used for the manufacture of HAS 5% and 25%. These equipment consist of (b) (4). However, these equipment are not used for the manufacture of other US licensed products. Please describe the controls to prevent contamination, cross-contamination and mix-ups; not limited to cleaning, removal of prions, containment, segregation, change-over and line clearance controls.

21)(b) (4) [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

17) Regarding (b) (4) [REDACTED] (Step (b) (4) – DP Manufacture Process) – Microbiological Lot Review from the batch records of Lots (b) (4) [REDACTED] in Section 3.2.R.

- a. It was noted that you reported only the sterility and endotoxin release testing results as “Pass” in this form. It was noted in both batch records that bioburden in-process testing was conducted in several (b) (4) [REDACTED] Drug Product manufacturing steps. Also, you conducted endotoxin testing and sterility testing during Drug Product manufacture and Environmental Monitoring (EM) during (b) (4) [REDACTED] step. However, the results from these testing and the EM were not documented in this form. Please explain the reason to not document all bioburden, endotoxin and sterility testing results from the respective (b) (4) [REDACTED] DP manufacturing steps; in addition, the EM results from the filling step in this form.

18) Regarding the summary reports PPQR /805/o/01/01 and PPQR/805/o/03/01 provided in Amendment STN 125644/o.3 (DATS #669524).

- a. It was noted that you did not provide the EM results in support for the filling of the PPQ lots. Please provide copy of these results in support for the filling of all PPQ lots. Ensure to include the acceptance criteria and sampling locations.
- b. You did not provide a description of the results in support for the filling, heat treatment and (b) (4) [REDACTED] of sub-lots (b) (4) [REDACTED] in the summary report PPQR/805/o/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 a description of the results in support for the filling, heat treatment, and (b) (4) [REDACTED] from these sub-lots.

- c. It is unclear the summary of all the deviations included summary reports PPQR /805/0/01/01 and PPQR/805/0/03/01. Please provide a narrative that describes these deviations and their action taken for their resolution.
- d. It was noted in Section 3.2.P.3.5.1 from the original BLA that bioburden in-process testing was conducted to (b) (4). However, these 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.

19) Regarding Sections 3.2.P.3.5.1, 3.2.P.7.1 and 3.2.P.8.3.1.

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 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.
- 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 to be use used during routine filling of HAS 5% and 25%.
- c. 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)]. It is so, please provide copy of the summary report from this CCIT.

20) Regarding summary report PQRo6800102, approved on November 2013 and provided in Amendment STN 125644/0.10 (DATS #675334). It was noted that the content of this report is the same as included in summary report PQRo68001 01, approved in January 2001. Therefore, it is unclear what the testing conducted in this PQ study. Please provide a complete description the PQ testing with acceptance criteria in support for PQRo6800102.

21) Regarding summary report PQR/524/0/01/0 provided in Amendment STN 125644/0.10 (DATS #675334). 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)

(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%.

22) Regarding summary report PQR482/o/o1/o1 provided in Amendment STN 125644/o.10 (DATS #675334).

- 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 (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 (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). If so; please provide a summary of this study with the results and acceptance criterion.

23) Regarding summary reports (b) (4) provided in Amendment STN 125644/o.10 (DATS #675334).

- a. You did not provide a complete description of the re-qualification runs at 60°C in both reports. It is unclear if these studies were conducted using a load of product or a “simulated load” of product. You also did not indicate the amount of thermocouples used and their location in these studies. In addition, it is unclear if you conducted any testing to determine the viral inactivation as part of these studies.
- b. Please provide a complete description of the re-qualification runs at 60°C conducted in both studies. Ensure to include, but not limited to a description of the load for these runs, amount of thermocouples used and their location in these runs. Also, please clarify if you conducted any testing for the inactivation of viruses in the load during these studies and during routine production.
- c. You stated that an incident associated with (b) (4) thermocouples that did not comply with the post-calibration error criterion of (b) (4). Please indicate the amount 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.
- d. You stated that Deviation QR93901 is 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). However, 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 QR93901.

24) Regarding summary report PQR/773/0/01/01 provided in Amendment STN 125644/0.10 (DATS #675334).

You stated that Deviation QR83855 was associated to a (b) (4) probes located in an empty (b) (4) did not comply with the criterion of (b) (4) . It is unclear if this (b) (4) was used in this study. 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 as acceptable, since a (b) (4) probes did not comply with the criterion of (b) (4) .

25) Regarding the summary of the aseptic filling simulation program provided in Amendment STN 125644/0.3 (DATS #669524).

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 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) ; in addition, to the actions to be taken in the case that there are changes in the aseptic filling of plasma-derived products in the AFS.
- b. Please corroborate if EM is conducted as part of the aseptic filling simulation studies.

26) Regarding Section 3.2.P.3.5.2.

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

a.

27) Regarding Section 3.2.A.1 from Original BLA and from Amendment STN 125644/0.5.

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 describe 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.

- 28) Regarding summary reports CVR/805/0/01/01 and CVR/748/0/02/01 provided in Amendment STN 125644/0.5. It is unclear if any testing has been conducted for the removal of prions from product contact equipment to be used in the manufacture of HAS 5% and 25%. Please clarify if any testing has been conducted in both studies; as well, during routine production in support for the removal of prions from product contact equipment to be used in the manufacture of HAS 5% and 25%. It is so, please indicate the testing with acceptance criteria and actions to be taken in the case that prions are detected in these equipment after cleaning.
- 29) Regarding summary report CVR/748/0/02/01 provided in Amendment STN 125644/0.5. You stated that the (b) (4) [REDACTED]. However, you did not stated the soiling and rinse solutions used in this study. Please indicate the soiling and rinse solutions used in this study.
- 30) It was noted that you did not provide a description of the sterilization process for upstream and downstream equipment ((b) (4) [REDACTED]) 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 ((b) (4) [REDACTED]) 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.
- 31) Regarding summary reports (b) (4) [REDACTED] provided in Amendment STN 125644/0.10.
- a. You did not specify the sterilizer/autoclave is 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) [REDACTED] 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) [REDACTED]: washers or sterilizers.

- 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.

5. Any new information requests to be communicated

- 1) Validation of the (b) (4) in 3.2.P.5.2 section 1.3.2
 - a. The information provided does not clearly state what type of (b) (4) method was used for determination of protein composition. Please provide detailed information for this method as described in FDA's "Analytical Procedures and Methods Validation for Drugs and Biologics" Guidance for Industry. This guidance is available on the FDA website.
 - b. Please provide representative images of the results.
- 2) Validation of (b) (4), 3.2.P.5.3 section 1.2.3.3:
 - a. In the linearity assessment, Table 29 (3.2.P.5.3 section 1.2.3.3 page 26), please explain what (b) (4) represents. Analytical Procedures (3.2.P.5.2 section 1.3.3 page 10) states that (b) (4) represent (b) (4) respectively, however page 28 (3.2.P.5.3 section 1.2.3.3) indicates that (b) (4) represents the (b) (4). Please explain the discrepancy.
 - b. Please clarify how many runs were done for robustness (Table 31, page 28, 3.2.P.5.3 section 1.2.3.3) testing for each modified condition.
 - c. Please provide representative (b) (4) (raw data) for the (b) (4) analysis of the final products. In addition, please provide calibration curve for the standards that was used in the analysis.
 - d. Please provide detailed information for System Suitability testing for the (b) (4) method.
- 3) Please explain the method you used for the determination of sodium. If it is an in house developed method, please provide detailed information for the method validation.

- 4) Please specify the (b) (4) you used at the (b) (4) line for the determination of sodium.
- 5) For the determination of Sodium Caprylate using (b) (4), please confirm if you have performed system suitability. Please also provide representative (b) (4).
- 6) For the method used for the determination of Sodium Acetyltryptophanate:
 - a. Please clearly define what type of (b) (4) method is used. Furthermore, please clarify whether you have performed System Suitability for the method.
 - b. Please provide representative (b) (4) (raw data) from the analysis.
 - c. Please confirm that you have measured the (b) (4) for (b) (4)-acetyl tryptophan to test the ability of the method to distinguish between the albumin (b) (4) and (b) (4)-acetyl tryptophan.
 - d. In the description of linearity assessment it is mentioned that a standard solution was used; however, the data in the table (table 46, page 39) shows results from different protein concentration of the 5% Albumin product. Please clarify the discrepancy. If standard solution is used, please give information about the source of the standard and the data found from the assessment.
- 7) For the determination of Aluminum using (b) (4):
 - a. Please specify the (b) (4) at which the (b) (4) of aluminium is measured.
 - b. For the linearity assessment, the linearity assessment was done using batch (b) (4) (25% Albumin product) with the addition of aluminum standard solution of (b) (4). However, the data provided in the table (table 57, page 48) are from a different batch and product ((b) (4), 5% Albumin product) with different amounts of aluminum standard solution added ((b) (4)). The plot of (b) (4) vs aluminum concentration for the data provided in the table loses linearity after the concentration of (b) (4) of Al, therefore the highest range limit should be this concentration of Al. Based on the observation on the data you provided in the table, (b) (4) are high concentrations and the correlation coefficient will not be in the limit. Please revise, or explain this assessment.
- 8) Please indicate the (b) (4) at which the (b) (4) were recorded in the analytical procedure and in the validation assessments. Please also provide the (b) (4) used for (b) (4) concentration calculation.

- 9) Please clarify which standard is used for the determination of (b) (4) in routine testing, the (b) (4) (mentioned in the 3.2.P.5.2 Analytical procedures section 1.5.5) or In House Control (mentioned in method validation for (b) (4) determination). If it is In House Control, please provide the description that contains:
- i. Preparation, storage, and stability of the standard
 - ii. Calibration against (b) (4)
10. The (b) (4) SOP you sent in response to my request for Albumin identity testing does not have information on the analysis of the (b) (4). Please provide details of the analysis and representative raw data (image).
11. The data generated for summary table 14 in section 3.2.S.2.6 is based on results of an (b) (4) assay that in which an expired (b) (4) was used. Please repeat this assay with a viable (b) (4) and submit the results.
12. Section 3.2.S.6 subsection 1.8 describes the (b) (4) step in the production of drug substance. Please describe the origin of the production batches listed in table 17.
- 6.** Proposed date(s) for the Late-Cycle meeting (LCM)
The proposed date for the late cycle meeting will be August 24, 2017 . Please indicate the communication preference for the late cycle meeting such as a teleconference or a face-to-face meeting. We intend to send the Late Cycle Meeting materials by August 22, 2017. If these timelines change, we will communicate updates to you during the course of the review.
- 7.** Updates regarding plans for the AC meeting
This application will not be reviewed by an advisory committee.
- 8.** Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.
Any milestone dates related to the remainder of the review cycle will be communicated once all responses to the outstanding information requests are addressed.

END