



February 7, 2017

Our STN: BL 125644/0

## **BLA FILING NOTIFICATION**

Bio Products Laboratory  
Attention: Mary Ann Lamb, PhD  
Bio Product 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) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated December 7, 2016, for Human Albumin Solution 5% and 25% to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The review classification for this application is Standard. Therefore, the review goal date is December 9, 2017. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which include the timeframes for FDA internal milestone meetings. We plan to hold our internal mid-cycle review meeting on May 25, 2017. Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process.

We will contact you regarding your proposed labeling no later than November 9, 2017. If post marketing study commitments (506B) are required, we will contact you no later than November 9, 2017.

We are not currently planning to hold an advisory committee meeting to discuss this application.

While conducting our filing review, we identified the following potential review issues:

1. The application lacks organizational elements. For example:
  - a. There is no Table of Contents that outlines the sections of your submission.
  - b. There is no 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 Human Albumin Solution 5% and 25% for Infusion.
  - c. FDA forms 3674, 3454, and Debarment certification were not included.
2. The application appears to contain contradictory and incomplete information. For example:
  - a. There are no facility diagrams that illustrate the area classification and differential pressure of the rooms used for the manufacture of Human Albumin Solution 5% and 25% for Infusion.
  - b. There is no narrative of the controls to prevent contamination, cross-contamination and mix-ups. For example:
    - i. There is no narrative of the containment, segregation, change-over and line clearance controls; as well, in-process controls implemented in your facility for the manufacture of plasma derived products;
    - ii. There is no narrative 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;
    - iii. There is no description of the general equipment design used for the manufacture of plasma derived products;
    - iv. There is no narrative of the cleaning and disinfection processes of the areas and equipment used for the manufacture of plasma derived products.
  - c. The application does not contain a description of other products manufactured. For example:
    - i. There is no list of dedicated, share and disposable (single-use) equipment used for the manufacture and packaging of US licensed products and for other markets;

- ii. There is no list of equipment that use automated systems;
  - iii. There is no list of rooms used for the manufacture and packaging of US licensed products and other markets.
  - iv. There is no list of existing and new equipment used for the manufacture and packaging of Human Albumin Solution 5% and 25% for Infusion.
- d. The application does not contain a narrative of the incoming procedure for the plasma and materials used for the manufacture of Human Albumin Solution 5% and 25% for Infusion.
  - e. The application does not contain a manufacturing and packaging flow chart that illustrates each manufacturing and packaging step.
  - f. The application does not contain a list and copies of the procedures used for the manufacture and packaging of Human Albumin Solution 5% and 25% for Infusion lot.
  - g. The application does not contain copies from the batch records of Human Albumin Solution 5% and 25% for Infusion lots manufactured.
  - h. The application does not contain a narrative of the shipping process from the plasma collection sites to the manufacturing facility.
  - i. The application does not contain a narrative of the equipment used for the manufacture and packaging processes for Human Albumin Solution 5% and 25% for Infusion.
  - j. The application does not contain a narrative of the vial inspection, labeling and packaging processes for Human Albumin Solution 5% and 25% for Infusion.
  - k. The application does not contain a narrative of the aseptic filling simulation program in their facility for the manufacture of plasma derived products.
  - l. The application does not contain summary reports of the aseptic filling simulation studies in support for the filling of Human Albumin Solution 5% and 25% for Infusion.
  - m. The application does not contain summary reports of the Performance Qualification studies for the equipment used for washing, sterilization and depyrogenation of components in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion.

- n. The application does not contain summary reports of the Performance Qualification studies for the process equipment used for the manufacture and packaging of Human Albumin Solution 5% and 25% for Infusion.
- o. The application does not contain summary reports of the Process Validation and Cleaning Validation studies in support for Human Albumin Solution 5% and 25% for Infusion.
- p. The application does not contain summary report of the Container Closure Integrity Test (CCIT) in support for Human Albumin Solution 5% and 25% for Infusion.
- q. The application does not contain a narrative of water and Heating, Ventilating, Air Conditioning (HVAC) systems. For example:
  - i. There is no narrative of these systems;
  - ii. There is no narrative of changes done in these systems in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion;
  - iii. There is no narrative that describe the Environmental and Water Monitoring Programs with their acceptance criteria;
  - iv. There are no Environmental and Water Monitoring Results in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion;
  - v. There are summary reports of the Qualification studies done in these systems in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion.
- r. The application does not contain a narrative of facility systems (for example, facility/alarm monitoring system). For example:
  - i. There is no narrative of changes done in these systems in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion;
  - ii. There are summary reports of the Qualification studies done in these systems in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion.

Based upon the above stated issues, we recommend that Bio Product Laboratory Ltd. amend this application with the following information:

1. A Table of Contents that clearly outlines each section of the submission (such as facility, equipment, processing validation, analytical testing verification, etc.).
2. An Introduction Section that outline 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 and packaging of Human Albumin Solution 5% and 25% for Infusion.
3. A summary narrative that clearly and concisely describes the changes in your facility and manufacturing and packaging processes in support for the manufacture and packaging of and packaging of Human Albumin Solution 5% and 25% for Infusion. In addition, this narrative has to identify the relevant activities you have performed to support the manufacture of this product. You should also provide summaries of all validation and qualification reports including summarized outcome data in this document as well as provide the original reports as attachments in the appendix section. Each report should include an independent Table of Contents identifying page numbers of important sections in the report (for example, results, attachments, etc.). Please also be sure to review all documents for legibility before including them in the submission.
4. A summary narrative that clearly and concisely describes the controls to prevent contamination, cross-contamination and mix-ups in your manufacturing facility. Ensure to provide a description of general equipment design; containment, segregation, change-over and line clearance controls; as well, in-process controls implemented in your facility for the manufacture of plasma derived products. Please provide a 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. In addition, please include a narrative of the cleaning and disinfection processes of the areas and equipment used for the manufacture of plasma derived products.
5. A summary narrative that clearly and concisely describes other products manufactured in your facility. Ensure to provide a list of dedicated, shared and disposable (single-use) equipment used for the manufacture and packaging of US licensed products and for other markets. Please outline the equipment that use automated system; in addition to, existing and new equipment used for the manufacture and packaging of Human Albumin Solution 5% and 25% for Infusion in this list. Ensure to include the room number(s) where these equipment are located.
6. A summary narrative that clearly and concisely describes the incoming procedures for the plasma and materials used for the manufacture of Human Albumin Solution 5% and 25% for Infusion.

7. A summary narrative that clearly and concisely describes the shipping procedure of the plasma from the collection sites to your manufacturing facility. Ensure to describe if there have been any changes to the shipping process.
8. A manufacturing and packaging flow chart that illustrates each manufacturing and packaging step in support for Human Albumin Solution 5% and 25% for Infusion. Ensure to include the room where each step is conducted, the equipment used, procedures applicable to each step, test and in-process controls performed; in addition, to the methods used to transfer the product between steps.
9. A summary narrative that clearly and concisely describes the vial inspection, labeling and packaging processes for Human Albumin Solution 5% and 25% for Infusion.
10. A list and copies from the procedures used for the manufacture and packaging of Human Albumin Solution 5% and 25% for Infusion.
11. Copies from the batch records of Human Albumin Solution 5% and 25% for Infusion lots manufactured in support of this application.
12. Copies from the summary reports of the Process Validation studies in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion lots manufactured.
13. A summary narrative that clearly and concisely describes the Container Closure Integrity Test (CCIT) in support for Human Albumin Solution 5% and 25% for Infusion. Ensure to include the summary report of the CCIT in support for Human Albumin Solution 5% and 25% for Infusion.
14. A separate appendix (that includes the full reports having appropriate page numbering that are relevant to that section) for each of the sections listed below:
  - a. Facility:
    - i. A completed description of your facility with legible diagrams of the manufacturing and associated support areas. Room classification and pressure differentials should be identified for manufacturing areas. Process flows should be clearly identified including the manufacturing areas where each step of the manufacturing and packaging processes are occurring in the facility. A description of the measures used to prevent unauthorized access into the manufacturing areas should also be provided.
    - ii. A summary narrative that clearly and concisely describes water and HVAC system; in addition, to facility systems (for example, alarm and monitoring systems, etc.). Ensure to provide a description of

changes conducted in these systems in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion.

- iii. Summaries of the Qualification of your facility systems (for example, alarm and monitoring systems, etc.) and utilities with qualification reports as attachments in the correspondent appendix section to support the manufacture of Human Albumin Solution 5% and 25% for Infusion in your facility as intended.
- iv. A description of the cleaning/sanitization procedures including gowning practices for the manufacturing areas.
- v. A brief description of your Environmental Monitoring program, including monitoring for airborne viable and non-viable particles, surface sampling, frequency of the monitoring, and the alert and action levels established for each area. Ensure to include the Environmental Monitoring Results in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion.
- vi. A brief description of your water program, including monitoring, frequency of the monitoring, and the alert and action levels established for each type of water. Ensure to include the water Monitoring Results in support for the manufacture of Human Albumin Solution 5% and 25% for Infusion.
- vii. A summary of the validation(s) or verification(s) performed for all computer systems that control critical manufacturing processes to demonstrate that these systems operate as intended.

b. Equipment:

- i. A summary narrative that clearly and concisely describes the equipment used for washing, sterilization and depyrogenation of components; in addition, to all manufacturing and packaging equipment in support for Human Albumin Solution 5% and 25% for Infusion. Ensure to specify which equipment is new or existing and include the location of the equipment in the description or in diagrams.
- ii. A summary of the qualifications performed for the equipment used for washing, sterilization and depyrogenation of components; in addition, to all manufacturing and packaging equipment in support for Human Albumin Solution 5% and 25% for Infusion. Ensure to include full qualification reports as attachments or in the appendix section. The attachments to the qualifications should be clearly referenced and easily identifiable so that the information is clear and easy to find.

- iii. The procedures used for cleaning of manufacturing and packaging equipment in support for Human Albumin Solution 5% and 25% for Infusion, if new cleaning procedures or disinfectants are used, or a statement that the procedures/disinfectants are the same as other US licensed products.
- iv. A summary of the Cleaning Validation studies performed for the manufacturing equipment in support for Human Albumin Solution 5% and 25% for Infusion. Ensure to include full validation reports as attachments or in the appendix section. The attachments to the qualifications should be clearly referenced and easily identifiable so that the information is clear and easy to find.
- v. A summary narrative that clearly and concisely describes the aseptic filling simulation program in their facility for the manufacture of plasma derived products.
- vi. A summary of the aseptic filling simulation studies performed in support for the filling of Human Albumin Solution 5% and 25% for Infusion. Ensure to include full validation reports as attachments or in the appendix section. The attachments to the qualifications should be clearly referenced and easily identifiable so that the information is clear and easy to find.

Refer to the following guidance for additional information:

*Guidance for Industry – For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum Derived Products* (February 1999).

15. Please submit:

- a. FDA Form 3674 with authorized signature
- b. Financial disclosure forms FDA 3454 and or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)
- c. Debarment Certification form.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we

shall advise you in writing of any action we have taken and request additional information if needed.

If you have any questions, please contact Lorraine Wood at (240) 402-8439 or at [lorraine.wood@fda.hhs.gov](mailto:lorraine.wood@fda.hhs.gov).

Sincerely,

Iliana Valencia, MS  
Chief, Regulatory Project Management Staff  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research