Summary Basis for Regulatory Action

Date: June 19 2018

From: Wayne Hicks, Review Committee Chair

BLA STN# :125644/0

Applicant Name: Bio Products Laboratory

Date of Submission: December 9, 2016

PDUFA Goal Date: June 19, 2018

Proprietary Name/ Established Name: Albuminex/Albumin (Human) 5% and 25%

Indication: Hypovolemia, prevention of central volume depletion after paracentesis due to cirrhotic ascites, hypoalbuminemia from burns, acute nephrosis, adult respiratory distress syndrome

Recommended Action:
The Review Committee recommends approval.

Review Office(s) Signatory Authority(ies): Nicole Verdun**,** Acting Office Director, OBRR

☐ **I concur with the summary review.**
☐ **I concur with the summary review and include a separate review to add further analysis.**
☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)*	Wayne Hicks, 6/14/2018 Tigist Kassa, 4/25/2018 Michael Strader 4/25/2018

	Priscilla M. Pastrana 5/1/2018
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Charles Maplethorpe Wei, Shaokui 5/2/2018 BIMO review/inspection waived
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Linye Song 5/2/2018
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Jin Hyen Baek 5/1/2018
Clinical Pharmacology Review(s)	Not applicable for this submission
Labeling Review(s) • *APLB (OCBQ/APLB)*	Alpita Popat 6/5/2018
• OCBQ/DBSQC	Sean Younker, 5/1/2018 Karen Smith, Hyesuk Kong, Varsha Garnepudi. 5/1/2018

1. INTRODUCTION

Bio Products Laboratory (BPL) submitted this original Biologics License Application (BLA) for licensure of albumin, human-kjda 5% and 25% solution for infusion with the proprietary name ALBUMINEX. ALBUMINEX is manufactured using a (b) (4) method. The product is packaged as a sterile liquid formulation in single use vials suitable for intravenous use.

The Indications for ALBUMINEX are hypovolemia, ascites, hypoalbuminemia including from burns, acute nephrosis, acute respiratory distress syndrome and cardiopulmonary bypass.

2. BACKGROUND

Meetings with FDA:

A pre-BLA meeting was scheduled for May 8, 2014 to discuss the content of the BLA application. FDA provided written pre-meeting responses dated April 30, 2014, which BPL found adequate and clear, such that the pre-BLA meeting was cancelled. FDA agreed that a summary of published medical literature would provide sufficient clinical data to support the review of the application.

Submission Chronology:

The application was received on December 9, 2016, and review was conducted under the PDUFA V review schedule. Following several Information Requests, a Complete Response letter was issued on August 25, 2017 due to multiple deficiencies in the Chemistry Manufacturing and Controls (CMC) section of the submission. BPL responded to the Complete Response letter on December 15, 2017 by submitting an amendment to the original application.

Albumin Protein (General)

Albumin constitutes about half of the proteins, by mass, in blood plasma. It is a monomeric, blood soluble protein that performs several biological functions. Albumin maintains oncotic pressure, and serves as transport protein for various fatty acids, growth factors, chaperones, metal ions, and toxic substances. The normal concentration of albumin in blood is about 35 – 50 g/L. In addition to its use as a colloid replacement solution, albumin is used as an excipient and to increase the stability and half- life of other therapeutics.

Albumin (Human) Manufacturing

Albumin (Human) can be produced by recombinant methods, however it is most commonly purified from human plasma. Purification of albumin from plasma is generally performed by two different fractionation methods, and variations thereof. The Cohn method uses the approach of modifying the pH, cold ethanol precipitation, and centrifugation into five (V) fractions to enrich for albumin. Albumin is produced from Fraction V. The Kistler-Nitschmann fractionation process is a variation of the Cohn process which reduces the volume and amount of ethanol used by eliminating Fraction IV.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

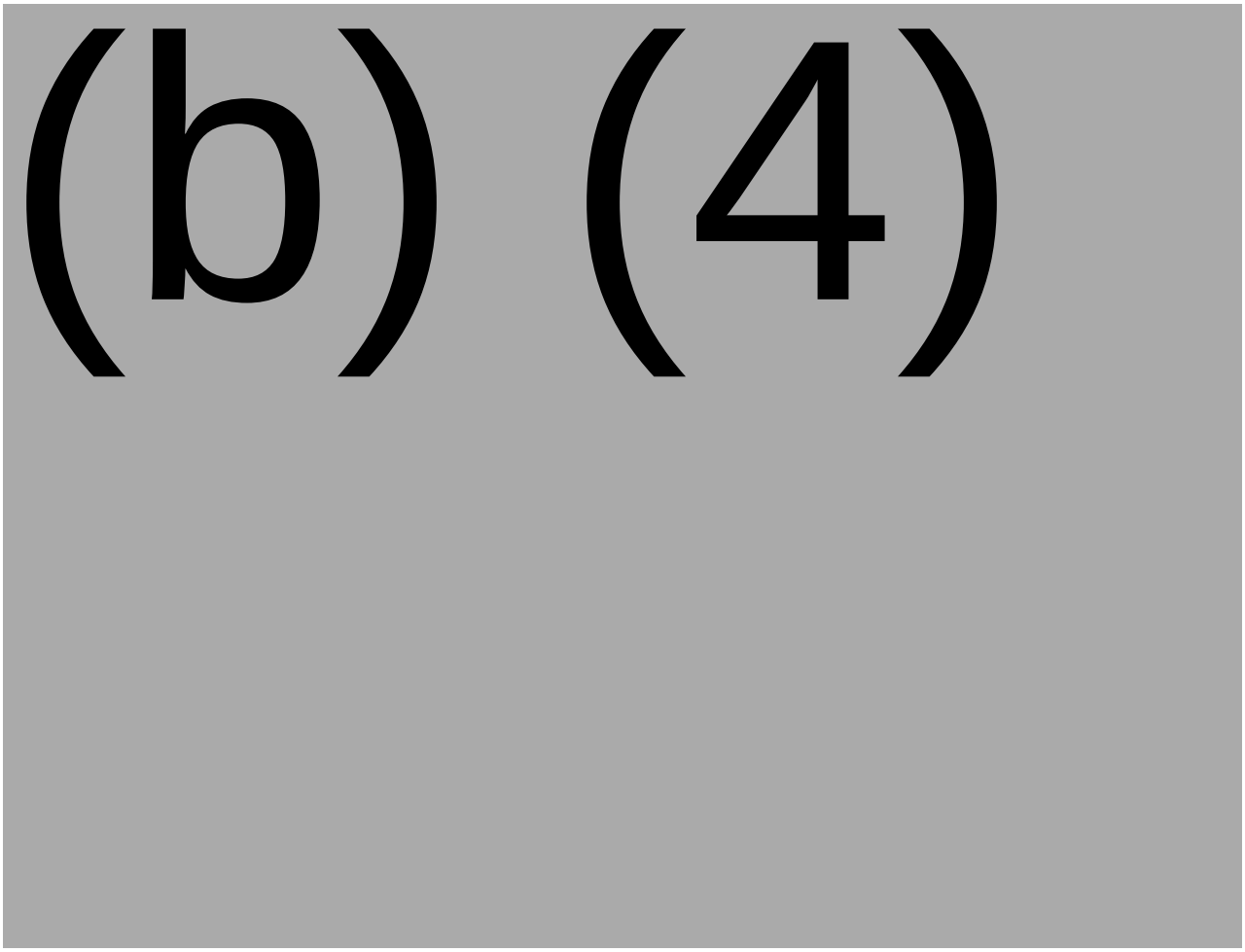
Manufacturing Summary:
Bio Products Laboratory manufactures Albumin (Human) at two concentrations, 5% and 25%, using (b) (4) Plasma collected at FDA licensed collection centers located in the United States. Plasma is collected from donors screened for eligibility based on their health status. Individual plasma units are stored at (b) (4) and remain in a (b) (4) through pooling at BPL. Plasma pools are tested for viruses using nucleic acid test methods and immunoassays to detect viral antigens and antibodies as summarized in Table 1.

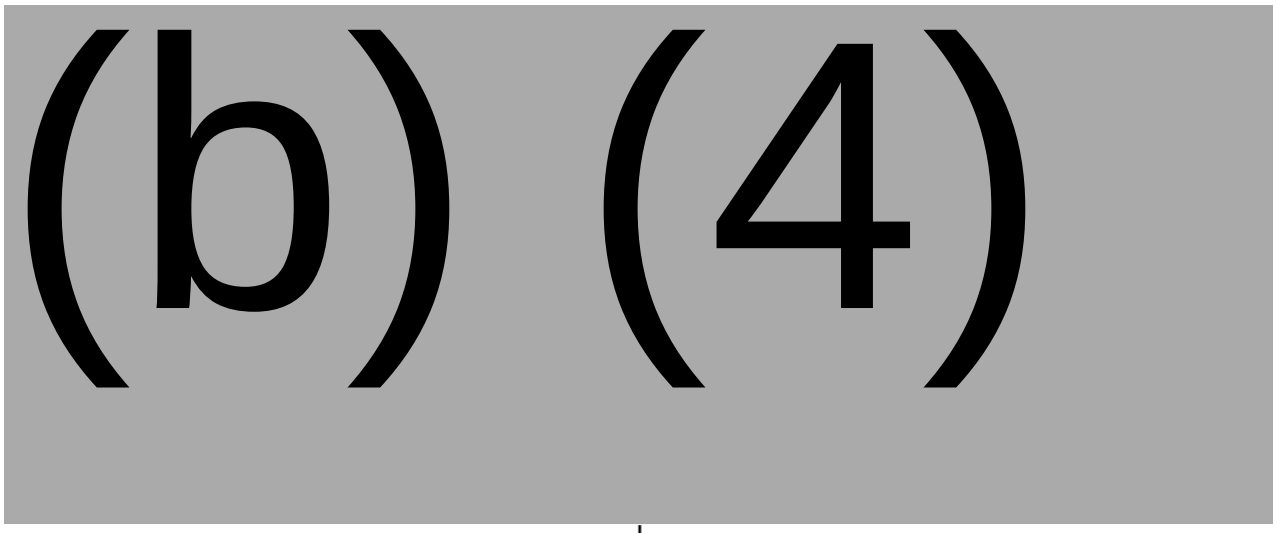
Table 1. Tests Carried out on Plasma Pools

(b) (4)

The following scheme shown in Figure 1 provides an overview of the plasma fractionation process and manufacturing steps up to the production of the drug product.

Figure 1 Manufacturing Scheme - Plasma to Drug Product





Filling and Finishing	Step (b) (4)	Filling
	Step	(b) (4)
	Step	
	Step	Inspection
	Step	Labeling and packaging
	Step	Identity testing
	Step	Drug Product

In-Process Controls:
Safety risks are mitigated using in-process controls and establishment of critical process parameters. In-line process control testing is performed during manufacturing to monitor critical process parameters and product quality. This includes measuring the concentrations of (b) (4) .

Batch Analysis:

Summary table data was provided for in-process control testing during full scale manufacturing. Specification limits were retroactively applied; however, results are very similar for the performance qualification (PQ) batches. This supports the consistency, and control of the manufacturing process.

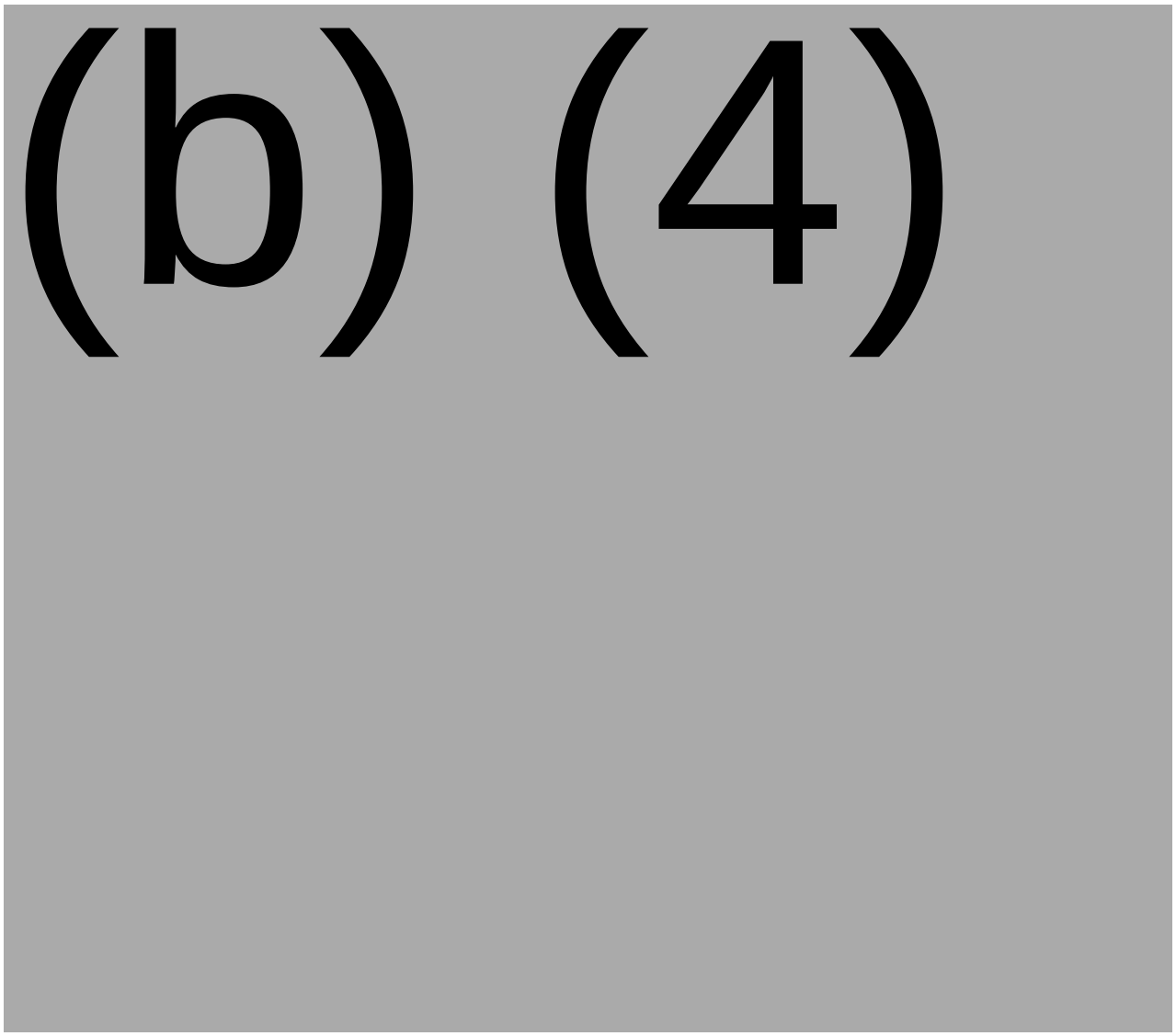
Adventitious Agents:

There are no process steps designed specifically for removal of adventitious agents. However, the precipitation steps were evaluated using scaled down models for their ability to remove viruses and TSE (prion) agents.

Viral Reduction

Figure 2 shows the manufacturing steps that are considered by the manufacturer to be effective in viral reduction.

Figure 2



The following evaluations were performed at various manufacturing steps to assess viral reduction.

- Investigation of (b) (4) of viruses
- Evaluation of virus removal/(b) (4) during (b) (4) of viruses

- Evaluation of virus removal (b) (4) at A+1 precipitation step: Infectious Bovine Rhinotracheitis (IBR), Hepatitis A virus (HAV) and Sindbis virus
- Development and evaluation of a small-scale model of the albumin Fraction IV (Fr-IV) fractionation process
- Evaluation of virus removal /(b) (4) during the Fr-IV process
- Robustness of virus removal/(b) (4) during Fr-IV process
- Toxicity and interference of the new formulation of albumin on model viruses
- Virus inactivation in (b) (4) 5% and 25% albumin by Pasteurization
- Validation of the inactivation of Human Immunodeficiency Virus (HIV) by Pasteurization in the manufacturing process of 5% and 25% albumin

Tables 2 and 3 summarize the viral reduction achieved during two of the (b) (4) precipitation steps and Pasteurization (b) (4). The information provided in the original submission did not establish viral clearance for HIV that employed at least two major and independent viral clearance steps where each clearance step provides > 4 logs of clearance. BPL only provided clearance data for HIV during the Pasteurization step. Following issuance of the CR letter, this issue was addressed in the resubmission package submitted on December 18, 2017. BPL also provided data for the precipitation steps. The information provided by BPL in response to the CR letter was found to be sufficient.

Table 2. Virus Reduction Summary 5% Albumin (Human) Enveloped Viruses

Step	Reduction (log_{10})			
	HIV-1	Sindbis	BVDV	IBR
A+1 Precipitation[G]	nd	4.1[B]	>3.4[C]	3.4[B]
Fraction IV Precipitation	nd	>7.1[D]	>4.2[D]	>5.7[D]
Pasteurisation	>6.7[E]	>6.4[F]	>4.2[F]	>5.4[F]
Total	>6.7[A]	>13.5	>8.4	>11.1

nd, not determined.

[A] When minimum estimates for A+1 and Fraction IV for other model enveloped viruses are included, this gives a total of (b) (4) log

Table 3. Virus Reduction Summary 25% Albumin (Human) Enveloped Viruses

Step	Reduction (log_{10})			
	HIV-1	Sindbis	BVDV	IBR
A+1 Precipitation[G]	nd	4.1[B]	>3.4[C]	3.4[B]
Fraction IV Precipitation	nd	>7.1[D]	>4.2[D]	>5.7[D]
Pasteurisation	>6.6[E]	>6.2[F]	>4.0[F]	>5.0[F]
Total	>6.6[A]	>13.3	>8.2	>10.7

nd, not determined.
[A] When minimum estimates for A+1 and fraction IV for other model enveloped viruses are included, this gives a total of (b) (4) log

Viral clearance of manufacturing process steps was validated by small scale validation studies using model viruses. Virus models included HIV-1, IBR, which served as model for enveloped DNA viruses, Sindbis virus, Bovine Viral Diarrhea virus (BVDV) as a model for (b) (4), Hepatitis C virus (HCV), and Canine parvovirus which was included as a model for Parvovirus B-19.

Cytotoxicity assays were also performed. Samples of product from manufacturing steps modeled for viral clearance studies were quantitatively analyzed for virus content using a (b) (4) assay, and/or (b) (4) analysis. The conditions of viral analysis were adapted to the specifications of the manufacturing process being analyzed for viral clearance.

Prion Removal

The removal of adventitious agents during manufacture of Albumin (Human) includes removal of the agent known to cause Scrapie in sheep and goats, and those associated with Creutzfeldt-Jakob Disease (CJD), variant CJD (vCJD) and Transmissible Spongiform Encephalopathy (TSE).

(b) (4)

Analytical Procedures and Method Validation:

Analytical procedures and method validation reports for the manufacturing process were reviewed. During the review process, several information requests (IRs) were sent to the sponsor regarding method validation reports for determination of total protein by (b) (4), protein composition by (b) (4), determination of aluminum content by (b) (4), and determination of (b) (4). BPL responses received after the CR letter dated August 25, 2017, satisfactorily addressed the concerns mentioned in the CR letter and updated the analytical procedures and validation reports.

Method validation for (b) (4) determination was initially found to be inadequate for accuracy, repeatability, and intermediate precision. This was due to an inadequate number of samples that were used for testing and the use of samples with concentrations exceeding reported detection limits.

BPL successfully addressed the accuracy issues following resubmission and accuracy validation testing met specifications. (b) (4) determinations were performed on (b) (4) separate samples spiked with (b) (4) different levels of (b) (4) standard. Accuracy was met for the specification limit of (b) (4). However, repeatability and intermediate precision failed due to the use of real final product samples with low levels of (b) (4) that were well below the detection limit and specification limit. Since the accuracy data indicates that the method is capable of quantifying (b) (4) near the specification limit, and the final samples contain very low (b) (4) levels; a post-marketing commitment (PMC) for revalidation of the (b) (4) assay was agreed upon. BPL has been directed to use standard samples rather than real samples for revalidating repeatability and intermediate precision.

Release Specifications:

Tables 4 and 5 list final release specifications for the final drug product. The limits are in agreement with those of other Albumin (Human) products and those listed in the 21 CFR 640.82. The compliance reference column in Table 4 indicates whether the values given in the limits column were specified by the indicated CFR code, the USP code, or a specification developed by BPL.

Table 4. Albumin (Human) 5% and 25% Drug Product Specification Tests

	Test	Limits		Compliance Reference
		5%	25%	
Characteristics	pH at +20°C	6.4-7.4		CFR 640.82
	Appearance of Solution	Clear, slightly viscous liquid, almost colorless, yellow, green or amber.		BPL
	Albumin Identity	Main component of the preparation corresponds to the main component of human serum.		BPL
Biological Safety Tests	Endotoxin, EU/mL	(b) (4)		(b) (4)
	Sterility	Pass		
Purity/Specific Function	Protein g/L, HAS 5% only	(b) (4)		CFR640.82
	Protein Composition % Albumin	NLT 96		CFR 640.82
	(b) (4)	(b) (4)		BPL
	Thermostability test (57°C for 50 hours)	No visual change		CFR 640.82
Excipients	Sodium mmol/L[A]	130 - 160		CFR 640.82
	Caprylate mmol/L	(b) (4)		CFR 640.81
	Acetyltryptophanate, mmol/L			CFR 640.81
Impurities	(b) (4)	(b) (4)		BPL
	Aluminum, µg/L	NGT 200		BPL
	Potassium, mmol/L[A]	NGT 2		CFR 640.82
	(b) (4)	(b) (4)		(b) (4)
				BPL

[A] mmol/l value equal to mEq/L value
NGT Not Greater Than
NLT Not Less Than

Specification testing is also carried out on the labeled product according to the methods listed in the following table.

Table 5. Albumin (Human) 5% and 25% Labelled Product Specification Tests

	Test	Limits		Compliance Reference
		5%	25%	
Purity/Specific Function	Total Protein, g/L	(b) (4)		CFR 640.82
	Protein Composition % Albumin	NLT 96		CFR 640.82

NLT Not Less Than

Drug Substance and Final Drug Product Stability Characterization:

The drug substance for ALBUMINEX (albumin, human – kjda) 5% and 25% is the (b) (4) . The drug product is processed from the drug substance first by (b) (4) for ALBUMINEX (albumin, human – kjda) 25% and (b) (4) for ALBUMINEX (albumin, human – kjda) 5%. (b) (4) . The bulk drug product is then filled into (b) (4) glass vials (b) (4) .

(b) (4) . Drug product stability characterization includes parameters chosen in accordance with the International Council for Harmonization (ICH) recommendation. The principal stability indicating parameters selected include the (b) (4) as measured by (b) (4) . Visual appearance, pH, sodium acetyltryptophanate, aluminum and (b) (4) are monitored throughout.

Initial review of the data provided in the original application revealed a lack of raw data accompanying the summary tables for stability studies and the impurity profile, and a lack of detail in the drug substance characterization data. Information requests sent to BPL were satisfactorily addressed.

Section 3.a: CMC Product Quality

Testing specifications

The analytical methods and their validations and/or qualifications reviewed for ALBUMINEX (albumin, human – kjda) 5% and 25% drug products were found to be adequate for their intended use.

Section 3.b:

CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

Section 3.c:

Facilities review/inspection

Facility information and data provided in this BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of the products in

this BLA is listed in the table below. The activities performed and inspectional history is noted in the table and further described in the paragraphs that follow.

Table No. 6: Facility Information and Inspectional History

Name/Address	FEI number	DUNS number	Results/Justification
Drug Substance *Drug Product* *In-Process and Release Testing* Bio Product Laboratory Ltd. Dagger Lane, Elstree, Hertfordshire WD6 3BX United Kingdom	1000184635	216845337	Team Biologics January 26 – February 02, 2017 VAI

Team Biologics performed a surveillance inspection of the Hertfordshire, United Kingdom facility from January 26 - February 02, 2017. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

Section 3.d:

Environmental Assessment

This BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

Section 3.e:

Container/Closure

The albumin, human-kjda solution is filled into the following (b) (4) glass bottles with 32mm neck supplied by (b) (4):

Table No. 7: Bottle Sizes Used for the Container/Closure of HAS 5% and 25% Drug Product

DP	Bottle Sizes	Dosage
albumin, human – kjda 5%	(b) (4)	12.5 g
		25 g
albumin (Human) 5%		12.5 g
		25 g

A 32-mm diameter halobutyl rubber stopper ((b) (4)) is used to stopper the filled vial. Then the vial and stopper is sealed with a 32.5-mm (b) (4) aluminum overseal with a snap-off polypropylene cap ((b) (4)).

(b) (4) conducted the container closure integrity testing at their (b) (4) facility, employing the (b) (4) test method; all acceptance criteria were met.

Product Comparability

ALBUMINEX (albumin, human -kjda) 5% and 25% are comparable to, and made from the (b) (4) as Zenalb® 4.5% and 20%, respectively. The primary difference between ALBUMINEX (albumin, human -kjda) and Zenalb® is in the (b) (4), which are summarized in Table 8 below.

Table 8. Comparison of Key Specification Parameters for ALBUMINEX and Zenalb®

	Zenalb® 4.5	Zenalb® 20	Albuminex 5%	Albuminex 25%
Active ingredient				
Albumin g/L	45	200	50	250
In-active ingredient				
Sodium (mmol/L)	100-160	50-120	130 -160	130 -160
Potassium (mmol/g of protein)	(b) (4)		Not greater than 2	Not greater than 2
(b) (4)	(b) (4)		(b) (4)	
	(b) (4)			
Sodium caprylate (sodium n-octanoate) (mmol/L)	(b) (4)			
Sodium acetyltryptophanate (mmol/L)				
Aluminum (µg/L)	No more than 200	No more than 200	No more than 200	No more than 200

Source: BLA 125644/0, Section 2.5 Clinical Overview, Table 1 in Page 12

"Potassium (mmol/g of protein)" is a typing error by the sponsor. The correct statement is "mmol/L" specified in Section 3.2.P.5.1 of the submission "Specifications" to conform to 21 CFR 640.82.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The scope of the pharmacology/ toxicology review included extractables and leachables studies. An information request was sent to BPL for the extractables and leachables study. BPL provided the extractables study, but not a study on the leachables. A complete leachables study was requested as a Post-Marketing Commitment, by FDA.

Bio Products Laboratory committed to provide study results for leachables evaluated at the final shelf life for drug product ALBUMINEX (albumin, human) 5% and 25% as a post marketing commitment, and to submit study results within 36 months of approval.

5. CLINICAL PHARMACOLOGY

The following indications (from the proposed package insert) are sought for ALBUMINEX (albumin, human -kjda) 5%:

1.1 Hypovolemia

ALBUMINEX (albumin, human -kjda) 5% is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate e.g. hypovolemia following shock due to trauma or sepsis, in surgical patients and in other similar conditions with volume deficiency when restoration and maintenance of circulating blood volume is required in both adult and pediatric patients. In pediatric patients to reverse hypovolemia and achieve normal capillary refill time.

1.2 Ascites

ALBUMINEX (albumin, human -kjda) 5% is indicated for prevention of central volume depletion and maintenance of cardiovascular function after large volume paracentesis in patients with liver cirrhosis or other chronic liver disease in adults and children. ALBUMINEX 5% infusion plus administration of vasoactive drugs is indicated in the treatment of type I hepatorenal syndrome.
For patients with spontaneous bacterial peritonitis ALBUMINEX 5% is indicated as adjuvant treatment to antibiotic therapy.

1.3 Hypoalbuminemia Including from Burns

ALBUMINEX (albumin, human -kjda) 5% is indicated in patients with severe burn injury (> 20% total body surface area), but not until at least 12 to 24 hours after the burn, to correct protein loss, decrease overall fluid requirements, decrease systemic edema and stabilize cardiovascular hemodynamics without fluid overload (initial resuscitation should be with crystalloids).

1.4 Nephrotic syndrome

ALBUMINEX (albumin, human -kjda) 5% is indicated in patients with nephrotic syndrome in combination with loop diuretics to reinforce the diuretic therapeutic effect, which is reduced by hypoalbuminemia, and for the correction of reduced oncotic pressure.

1.5 Acute Respiratory Distress Syndrome (ARDS)

ALBUMINEX (albumin, human -kjda) 5% is indicated in conjunction with diuretics to correct fluid volume overload associated with ARDS.

1.6 Cardiopulmonary Bypass

ALBUMINEX (albumin, human -kjda) 5% is indicated in cardiopulmonary bypass procedures as part of the priming fluids to passivate the synthetic surfaces of the extracorporeal circuit and maintain the patient's colloid oncotic pressure.

The following indications (from the proposed package insert) are sought for ALBUMINEX (albumin, human -kjda) 25%:

1.1 Hypovolemia

ALBUMINEX (albumin, human -kjda) 25% is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate e.g. hypovolemia following shock due to trauma or sepsis, in surgical patients and in other similar conditions with volume deficiency when restoration and maintenance of circulating blood volume is required in both adult and pediatric patients. In pediatric patients to reverse hypovolemia and achieve normal capillary refill time.

1.2 Ascites

ALBUMINEX (albumin, human -kjda) 25% is indicated for prevention of central volume depletion and maintenance of cardiovascular function after large volume paracentesis in patients with liver cirrhosis or other chronic liver disease in adults and children. ALBUMINEX 25% infusion plus administration of vasoactive drugs is indicated in the treatment of type I hepatorenal syndrome.

For patients with spontaneous bacterial peritonitis ALBUMINEX 25% is indicated as adjuvant treatment to antibiotic therapy.

1.3 Hypoalbuminemia Including from Burns

ALBUMINEX (albumin, human -kjda)25% is indicated in patients with severe burn injury (> 20% total body surface area), but not until at least 12 to 24 hours after the burn, in order to correct protein loss, decrease overall fluid requirements, decrease

systemic edema and stabilize cardiovascular hemodynamics without fluid overload (initial resuscitation should be with crystalloids).

1.4 Nephrotic syndrome

ALBUMINEX (albumin, human -kjda) 25% is indicated in patients with nephrotic syndrome in combination with loop diuretics to reinforce the diuretic therapeutic effect, which is reduced by hypoalbuminemia, and for the correction of reduced oncotic pressure.

1.5 Acute Respiratory Distress Syndrome (ARDS)

ALBUMINEX (albumin, human -kjda) 25% is indicated in conjunction with diuretics to correct fluid volume overload associated with ARDS.

1.6 Cardiopulmonary Bypass

ALBUMINEX (albumin, human -kjda) 25% is indicated in cardiopulmonary bypass procedures as part of the priming fluids to passivate the synthetic surfaces of the extracorporeal circuit and maintain the patient's colloid oncotic pressure.

Summary of key clinical trials

At the pre BLA meeting, it was agreed that the clinical basis for licensure could be based on the submission of a review of the medical literature for the use of ALBUMINEX (albumin, human -kjda). The sponsor provided supporting literature for the indications proposed.
The literature that was reviewed to support the licensure of Albuminex 5% and 25% covered all the indications proposed. It was determined that the information provided was adequate to support approval of the application.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The sponsor did not perform any clinical studies to investigate the pharmacokinetics, efficacy, and safety of ALBUMINEX (albumin, human -kjda) 5% and ALBUMINEX (albumin, human -kjda) 25%.

b) Pediatrics

Pediatric Research Equity Act (PREA)

The initial Pediatric Study Plan (iPSP) and the Agreed PSP requesting full waiver were discussed at the October 19, 2016, and November 30, 2016, Pediatrics Research Committee (PeRC) meetings respectively. BPL's rationale for requesting a full waiver was supported by previous FDA decisions to release the PREA PMR for another

albumin product of the same class. BPL cited FDA Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans, March 2016, Procedural Revision 1, page 13, lines 327-328, *"Full or partial waivers previously granted for other drugs in the same class can be considered supportive information"*.

The PeRC agreed with BPL's rationale and plan to request a full waiver of the PREA requirements for all pediatric age ranges, for all indications for ALBUMINEX (albumin, human -kjda) under 21 CFR 601.27(c)(2)(ii) because the necessary studies would be impossible or highly impractical. FDA issued an Agreed Initial Pediatric Study Plan on December 2, 2016.

c) Other Special Populations

Clinical studies of ALBUMINEX (albumin, human -kjda) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

7. SAFETY

Albumin (Human) has a long-term record of safety. Based on published clinical safety data in literature and post-licensure studies, the sponsor delineated the important identified safety risks, important potential safety risks, and the important missing information (shown in Table 9).

Table 9.

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions, including anaphylactic or anaphylactoid reactions • Hypervolemia • Hemolysis
Important potential risks	• Transmission of infective agents such as viruses, emerging viruses, other unidentified infective agents or pathogens • Infusion of large volumes may have an adverse effect on coagulation or hematocrit.
Missing information	• No clinical trial experience in patients who are pregnant or lactating

Source: BLA 125644/0, Section 1.16 Risk Management Plan, Table 1, Page 9

The sponsor has proposed to use routine pharmacovigilance to monitor the safety of ALBUMINEX (albumin, human -kjda) 5% and ALBUMINEX (albumin, human -kjda) 25%. There are no ongoing or planned additional pharmacovigilance studies or activities. The proposed post-marketing pharmacovigilance actions for the identified safety concerns and missing information are summarized in Table 10.

Table 10: Summary of Safety Concerns and Planned Pharmacovigilance (PhV) Actions Proposed by the Sponsor

Safety concerns	**Proposed routine and additional PhV activities**	**Objectives**
Important identified risks: • Hypersensitivity reactions, including anaphylactic or anaphylactoid reactions • Hypervolemia • Hemolysis	Routine pharmacovigilance activities only. Important identified risk to be closely monitored and reports will be followed up by the sponsor	To achieve safe and effective use of ALBUMINEX 5% and ALBUMINEX 25% To ensure the Marketing Authorization Holder (MAH) collects data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in Individual Clinical Safety Reports (ICSRs)
Important potential risks: • Transmission of infective agents such as viruses, emerging viruses, other unidentified infective agents or pathogens • Infusion of large volumes may have an adverse effect on coagulation or hematocrit	Routine pharmacovigilance activities only. Important identified risk to be closely monitored and reports will be followed up by the sponsor	To achieve safe and effective use of ALBUMINEX 5% and ALBUMINEX 25% To ensure the MAH collects data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs

Missing information: • No clinical trial experience in patients who are pregnant or lactating	Routine pharmacovigilance activities – literature will be analyzed and outcomes data on exposure will be collected	To achieve safe and effective use of ALBUMINEX 5% and ALBUMINEX 25% To increase BPL's current knowledge of this missing information by identifying and analyzing data on outcome based exposures in pregnant patients or lactating mothers

The sponsor's proposed pharmacovigilance plan (PVP), was found to be acceptable. In addition, the important identified and potential risks will be noted under Section 5 Warnings and Precautions of the package insert.

8. ADVISORY COMMITTEE MEETING

No advisory committee was deemed necessary.

9. OTHER RELEVANT REGULATORY ISSUES

None.

10. LABELING

The proposed proprietary name, ALBUMINEX®, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on June 19, 2017, and was found acceptable. OBRR communicated the acceptability of the proprietary name to the applicant on July 12, 2017. The proper name, albumin, human - kjda was communicated to the sponsor on May 31, 2018.

The APLB found the FULL PRESCRIBING INFORMATION and carton/container labels for ALBUMINEX to be acceptable from a promotional and comprehension perspective. The review committee requested revisions to the PI and carton/container labels. The revisions are satisfactory.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review team unanimously recommended approval following resubmission. Approval was recommended with two PMC's.

b) Risk/ Benefit Assessment

Albumin, human has a long-term safety record. It has widespread clinical indications and shortages have been reported. The addition of a new supplier of albumin reduces the risk of shortages of this widely used therapeutic.

c) Recommendation for Postmarketing Activities

Two Post-marketing commitments were agreed upon with the company**.**

1. Bio Products Laboratory commits to provide study results for leachables evaluated at the final shelf life for drug product ALBUMINEX (albumin, human-kjda) 5% and 25% as a post marketing commitment, submitting study results within 36 months of approval. Final Report Submission: June 1, 2021.

2. Bio Products Laboratory commits to perform method validation for the determination of (b) (4) for intermediate precision using well characterized standards to establish valid range, repeatability, linearity and precision. In-process samples from the (b) (4) and final product samples should be tested against the result obtained using the established standards. Bio Products Laboratory Inc. will submit the results from the validation within six months of approval.

Application Type and Number: BLA/NDA BLA STN 125644/0

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COMMUNICATION TYPE: SBRA

History: Drafted: Wayne Hicks/

Concurrence:

Reviewed: Priscilla M. Pastrana (DMPQ)/ June 04, 2018
Reviewed: Michael Brad Strader (CMC)/June 04, 2018
Reviewed: Felice D'Agnillo/June 05, 2018
Reviewed: Wendy Paul/June 13, 2018, June 15, 2018
Reviewed: Orieji Illoh/June 14, 15, 2018

Office/Division	Name/Signature	Date
OBRR/DBCD	**Wayne Hicks**	**06/04/2018**
OBRR/DBCD	**Abdu Alayash**	**06/05/2018**

Office/Division	Name/Signature	Date
OBRR/DBCD	**Wendy Paul (for Orieji Illoh)**	**06/15/2018**
OCBQ/OD	**Mary Malarkey**	**06/18/2018**
OBRR/OD	**Nicole Verdun**	**6/18/2018**