

Memorandum

To: Wayne Hicks, Lead Reviewer LBVB/DBCD/OBRR/CBER

Lorraine Woods, RPMS/OMPT/OBRR/CBER

From: Michael Brad Strader, Ph.D., LBVB/DBCD/OBRR/CBER

Through: Abdu Alayash, Ph.D., LBVB/DBCD/OBRR/CBER

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Date: 05/12/2018

SUBJECT: Primary chemistry manufacturing and control (CMC) review of sections focused on Drug Substance and product characterization and stability for BL STN 125644 (Albumin), a Biologics License Application submitted by Bio Products Laboratory's (BPL) Human Albumin Solution (HSA).

RECOMMENDED ACTION: Approval. BPL responded adequately to IR requests sent on 04/18/17; no additional comments regarding these IRs were included in the Complete Response Letter. The sections in this review focused on drug substance characterization, stability and product stability are therefore approvable.

The submission (STN 125644) under review was dated December 9th, 2016, and the documents were submitted electronically and accessible in the EDR. My overview of the submission, summary, and recommended action are as follows.

EXECUTIVE SUMMARY: Drug Substance and Final Drug Product Stability Characterization

The drug substance for HSA 5% and 25% is the (b) (4) [REDACTED]. The drug product is processed from the drug substance by (b) (4) [REDACTED] for HSA 25% (b) (4) [REDACTED] for HSA 5%. (b) (4) [REDACTED]. The bulk drug product is then filled into (b) (4) [REDACTED] glass vials (b) (4) [REDACTED].

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

Upon review of sections focused on drug substance (3.2.S.2, 3.2.S.6, 3.2.S.4.4, 3.2.S.7) and product stability characterization (3.2.P.1, 3.2.P.2, 3.2.P.4, 3.2.3.P.5, 3.2.P.8), it was apparent that BPL often did not provide raw data, figures or plots to accompany summary tables listed in the submission. In addition, BPL did not provide SOPs or enough detail regarding the test methods and specification justifications for their characterization and stability studies. In response to these deficiencies, Information Requests (IRs) were sent on 04/18/2017 requesting a complete description (with raw data and figures) of all test methods listed for drug substance and product stability characterization and detailed justification for specification criteria. BPL was also asked to submit updated stability data for manufacturing scale and pilot batches for both HSA 5% and 25%. BPL's response (sent on 07/03/17) to all IRs related to drug substance and product stability characterization were complete and adequate for approval.

SUMMARY of SUBMISSION: This memorandum summarizes the review of drug substance and drug product characterization and stability for 5% and 25% HSA; (b) (4) [REDACTED] is the proposed name of the final product form. HSA is manufactured from (b) (4) [REDACTED] plasma collected in FDA-licensed plasma collection centers located in the United States.. The drug substance for HSA 5% and 25% is the (b) (4) [REDACTED]. The drug product is processed (See Figure 1 below) from the drug substance by (b) (4) [REDACTED] for HSA 25% and (b) (4) [REDACTED] for HSA 5%. (b) (4) [REDACTED]. The bulk drug product is then filled into (b) (4) [REDACTED] glass vials (b) (4) [REDACTED].

BACKGROUND: BPL currently manufactures (in Europe) human albumin at 45g/L (HSA 4.5%) and 200g/L (HSA 20%) as a single stabilizer (sodium caprylate), low salt human albumin product. For the US market a dual stabilizer formulation is required in the code of federal regulations (21 CFR §640.81), to accompany physiological sodium content and protein concentrations of 40, 50, 200 or 250g/L. Protein concentrations of (b) (4) [REDACTED] were selected as those most suited to the current commercial demand in the US market.

(b) (4)

Albumin is a plasma expander for treating patients who have suffered hemorrhage or shock. BPL's current single stabilizer albumin product Zenalb has been manufactured for over 20 years and the HSA 5% and 25% process is predominantly based upon this legacy product range. The (b) (4), is common to both HSA and Zenalb; however, HSA 5% and 25% have a different composition in the (b) (4) product. Zenalb is manufactured from human plasma sourced from US licensed collection facilities and (b) (4).

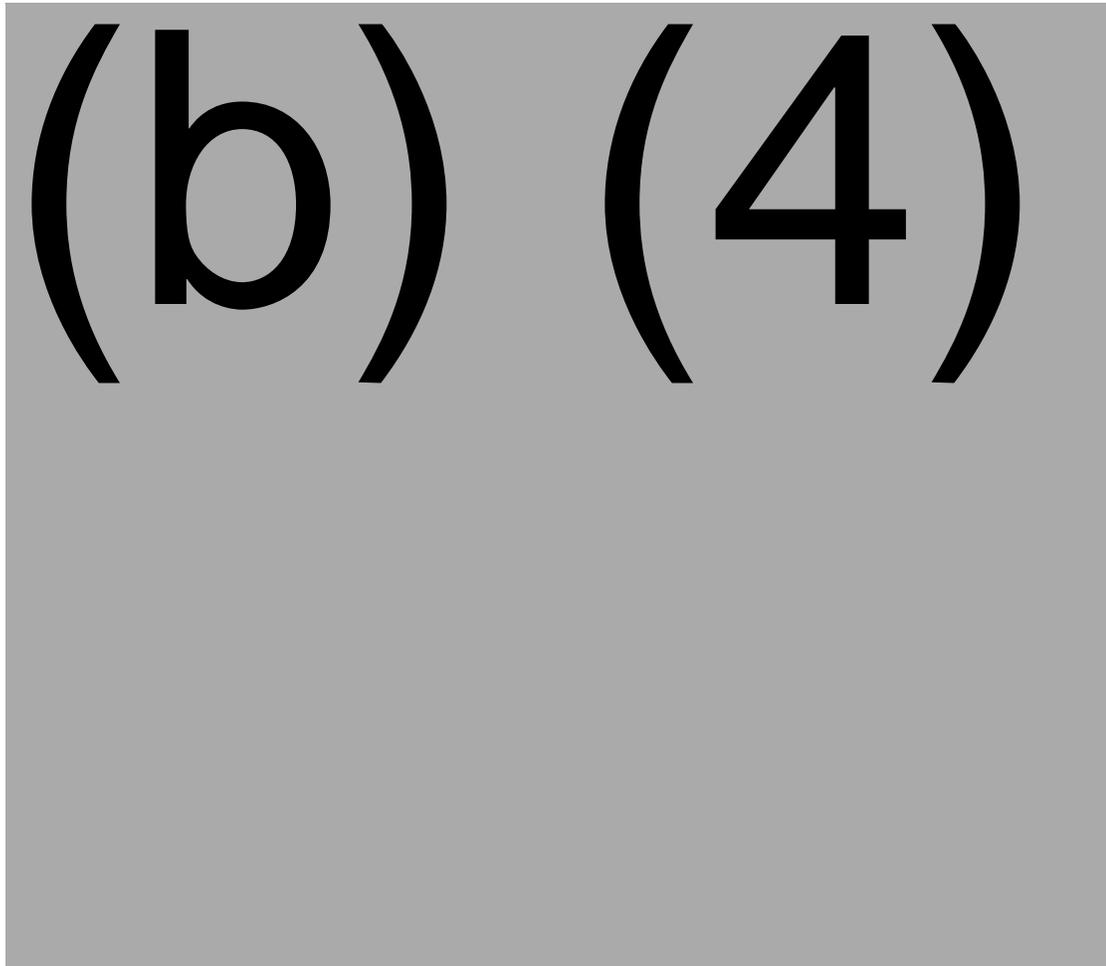
REVIEW SUMMARY

CHARACTERIZATION OF DRUG SUBSTANCE

(b) (4)

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CHARACTERIZATION OF DRUG PRODUCT STABILITY

[3.2.P.1] Description and composition of Drug Product: BPL’s Human Albumin Solution (HSA) 5% and 25% is Albumin (Human) sterile, aqueous solution for single dose intravenous administration. The composition of Human Albumin Solution (HSA) 5% and 25% drug product are shown in the tables show below respectively indicating the amount of each component per container unit. There is no overage.

Dosage Form

Human Albumin Solution (HSA) 25%
 Solution for Infusion 25%
 Presentations: 50 ml and 100 ml

Human Albumin Solution (HSA) 5%
 Solution for Infusion 5%
 Presentations: 250 ml and 500 ml

Table 1 Composition of HAS 25%

Component	50ml presentation	100 ml presentation	Function	Quality Standard
Human Albumin (protein (g))	12.5g	25g	Active Substance	(b) (4)
Sodium (g) / (mEq/L) ^A	(b) (4)		Isotonicity	
Caprylate (g)			Stabiliser	
Acetyl Tryptophanate (g)			Stabiliser	
(b) (4)			(b) (4)	

^A Sodium is principally derived from variable quantities of sodium (b) (4) added during formulation and sodium hydroxide added for pH adjustment.

Table 2 Composition of HAS 5%

Component	50ml presentation	500 ml presentation	Function	Quality Standard
Human Albumin (protein (g))	12.5g	25g	Active Substance	(b) (4)
Sodium (g) / (mEq/L) ^A	(b) (4)		Isotonicity	
Caprylate (g)			Stabiliser	
Acetyl Tryptophanate (g)			Stabiliser	
(b) (4)			(b) (4)	

^A Sodium is principally derived from variable quantities of sodium (b) (4) added during formulation and sodium hydroxide added for pH adjustment.

[3.2.P.2] Pharmaceutical Development: BPL has been manufacturing human albumin for over 20 years at 45g/L and 200g/L (product is Zenalb) as a single stabilizer (sodium caprylate), low salt human albumin product. For the US market a dual stabilizer formulation is required in the code of federal regulations (21 CFR §640.81), to accompany physiological sodium content and protein concentrations of 40, 50, 200 or 250g/L. Protein concentrations of (b) (4) were selected as those most suited to the current commercial demand in the US market. The active ingredient, Human Albumin, is common to both HSA and Zenalb; however, HSA 5% and 25% have a different (b) (4). Zenalb is manufactured from human plasma sourced from US licensed collection facilities and purified using (b) (4). The fractionated albumin is further purified by

(b) (4) [redacted]
 [redacted] . (b) (4) [redacted]
 process to give a final product with both sodium acetyltryptophanate and sodium caprylate at 0.08 millimole per gram of protein. (b) (4) [redacted]
 [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] A thorough review of the pharmaceutical development is provided by another CMC reviewer that focuses on manufacture process validation.

[3.2.P.4] Control of Excipients: All excipients (see Table below) used in the manufacture of Human Albumin Solution (HSA) 5% and 25% Drug Product are purchased to Pharmacopeial specification with a compliance certificate from the supplier. There are no excipients derived from Human or Animal origin used in manufacture of Human Albumin Solution (HSA). If a supplier cannot satisfactorily certify compliance to the pharmacopeia in-house testing is carried out to demonstrate compliance. In-house test methods are detailed for individual excipients and are in compliance with (b) (4) [redacted]. BPL in-house testing is limited to identity and microbial contamination (see description below).

Excipient	Specification
Sodium Hydroxide	(b) (4)
Sodium (b) (4)	[redacted]
(b) (4)	[redacted]
Caprylic Acid	[redacted]
(b) (4) -Acetyl-(b) (4)-Tryptophan	[redacted]

Analytical methods (In house methods if a supplier cannot satisfactorily certify Pharmacopeia compliance)

- 1. Sodium Hydroxide:** (b) (4) [redacted]
 [redacted]
 [redacted]
- 2. Sodium (b) (4)** [redacted]
 [redacted]
 [redacted]
- 3. Caprylic Acid:** (b) (4) [redacted] method is listed but not described.
- 4. (b) (4) -Acetyl-(b) (4)-tryptophan:** (b) (4) [redacted] method is listed but not described.

BPL indicated that (b) (4) [redacted] testing is performed for the excipients Sodium (b) (4) [redacted], Caprylic acid and (b) (4) -Acetyl-(b) (4)-tryptophan. These chemicals are not considered a microbiological (b) (4) [redacted] risk. However, if Pharmacopeia compliance is not established, BPL performs a limited amount of testing as per (b) (4) [redacted]. either by (b) (4) [redacted]
 [redacted] .

Normally, this will entail the testing of three consecutive batches from an individual supplier and if the results are satisfactory, testing of subsequent batches will not be carried out. If there is any reason for concern on the basis of the results obtained, then testing of subsequent batches will be continued.

[3.2.P.4] Drug Product Stability: The parameters chosen (see table below) to profile the stability characteristics of Human Albumin Solution (HSA) are in accordance with the recommendations of ICH *Topic Q5C, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*. The principal stability indicating parameters selected include the (b) (4) [redacted] as measured by (b) (4) [redacted]. Visual appearance pH, sodium acetyltryptophanate, aluminum and (b) (4) [redacted] are monitored throughout. The trial includes the test for (b) (4) [redacted] (expressed in terms of (b) (4) [redacted]), which is not part of the finished product specification, but which provides non-subjective supporting data to the visual assessment.

The sterility of each manufacturing scale batch is established during initial QC batch assessment and sterility assessment is also scheduled for end of trial. Microbiological assessment is not included for pilot scale batches as these were not filled in the manufacturing facility.

Test	Time points and temperatures tested (real time/(b) (4) [redacted])
Appearance of solution	Tested at all designated timepoints and temperatures
pH at 20°C	
(b) (4) [redacted]	
Sodium Acetyltryptophanate, mmol/L	
Aluminium, µg/mL	
(b) (4) [redacted]	Tested as minimum at 12, 24 and 36 month timepoints for +5°C, +25°C and +30°C storage
(b) (4) [redacted]	
(b) (4)Endotoxin, EU/mL*	
Total Protein (albumin) g/L	
Protein composition, albumin %	
Sodium, mmol/L	
Sodium Caprylate ((b) (4) [redacted]), mmol/L	
Potassium, mmol/L	
(b) (4) [redacted]	Tested at 36 month timepoint for +30°C storage
(b) (4) [redacted]	
Sterility*	

*Not assessed for pilot scale batches.

Stability data amounting of up to 12 months real time have been provided on (b) (4) [redacted] pilot scale batches of Albumin Human (5%), and (b) (4) [redacted] pilot scale batches of Albumin Human (25%). Data amounting of up to 6 months real time have been provided on (b) (4) [redacted] manufacturing scale batches of Albumin Human (25%). Data amounting of up to 3 months real time have been provided on (b) (4) [redacted] manufacturing scale batches of Albumin Human (5%) and (b) (4) [redacted] manufacturing scale batches of Albumin Human (25%). Batches encompass all concentrations and fill volumes.

At the routine storage temperatures of +5°C, +25°C and +30°C the batches have been found to be in compliance with all key stability tests meeting specification. No noticeable difference in profile is seen between the pilot scale and manufacturing scale batches, including at the accelerated (b) (4) condition. Data indicate that the batches will continue to meet specification to 36 months at both +5°C, +25°C and +30°C. The data therefore support a shelf life of 36 months at +5°C to +30°C.

Table 1 Summary of Human Albumin 5% Batches on Shelf-Life Stability

Batch	Purpose	Dose	Date of Fill	Vials Filled	Stability Trial Start Date	Data available
(b) (4)	PPQ Batch	(b) (4)	(b) (4)	(b) (4)	16 May 2016	3 months
	PPQ Batch	12.5g			20 May 2016	3months
	PPQ batch	25g			24 May 2016	3 months
	PPQ Batch	25g			24 May 2016	3 months
	PPQ batch	12.5g			27 Oct 2016	0 months

Table 2 Summary of Human Albumin 5% Pilot Scale Batches on Shelf-Life Stability

Batch	Purpose	Dose	Date of Fill	Vials Filled	Stability Trial Start Date	Data available
(b) (4)	Pilot Batch	25g	(b) (4)	(b) (4)	22 June 2015	12 months
	Pilot Batch	12.5g			06 July 2015	12 months
	Pilot Batch	12.5g			21 Aug 2015	12 months

Table 3 Summary of Human Albumin 25% Manufacturing Scale Batches on Shelf-Life Stability

Batch	Purpose	Dose	Date of Fill	Vials Filled	Stability Trial Start Date	Data available
(b) (4)	Development Batch	25g	(b) (4)	(b) (4)	27 Jan 2016	6 months
	Development Batch	25g			27 Jan 2016	6 months
	PPQ Batch	25g			17 May 2016	3 months
	PPQ batch	25g			17 May 2016	3 months
	PPQ Batch	12.5g			26 May 2016	3 months
	PPQ Batch	12.5g			26 May 2016	3 months
	PPQ Batch	25g			12 Oct 2016	0 months

Table 4 Summary of Human Albumin 25% Pilot Scale Batches on Shelf-Life Stability

Batch	Purpose	Dose	Date of Fill	Vials Filled	Stability Trial Start Date	Data available
(b) (4)	Pilot Batch	25g	(b) (4)	(b) (4)	09 Jun 2015	12 months
	Pilot Batch	12.5g			12 Jun 2015	12 months
	Pilot Batch	12.5g			27 Jul 2015	12 months

[3.2.P.4] Drug Product Stability: Stability testing for drug product should be performed on the proposed in-use period (BPL proposes a shelf-life of 36 months for HSA 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 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% HSA.

The following IR was sent:

Section 3.2.P.8 (Product stability Data)

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 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.

Reviewer comments: On July 11th, BPL responded adequately to the above IR by providing finished product stability data updated for 9 month and 12 months for 5% and 25% HAS for both proposed product and pilot batches. At routine storage temperatures of +5°C, +25°C and +30°C, the batches have been found to be in compliance with all key stability indicating tests meeting specification. No noticeable difference in profile is seen between the pilot scale and manufacturing scale batches, including at the accelerated (b) (4) condition.