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**Subject:** Final Review of Chemistry, Manufacturing and Controls, In-Process controls, and Manufacturing review of BLA for STN 125644 from Bio Products Laboratory for production of Human Albumin Solution 5% and 25%

**To:** Lorraine Wood, RPMS, OBRR, CBER (240) 402-8439

**Recommended Action:** Approval is recommended with a PMC.

<b>Reviewer</b>	<b>Discipline</b>
Wayne Hicks	Chair, CMC
Brad Strader	CMC
Tigist Kassa	CMC
Priscilla Pastrana	DMPQ
Amanda Trayer	DMPQ RPM
LinYE Song	Biostatistics
Chunrong Cheng	Biostatistics
Shokui Wei	OBE/Epidemiology
Alpita Popat	APLB Labeling Promotional
Jin Baek	Pharm.Tox
Charles Maplethorpe	Clinical Reviewer
Sean Younker	DSBQC/OCBQ
Varsha Garnepudi	Lot Release
Christine Drabick	Proprietary Name Review
Deepa Arya	BIMO

Submission Received:  
STN: 125644  
Sponsor: Bio Products Laboratory  
Submission type: Biological License Application  
Manufacturing Facility:

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**Post Marketing Commitment (125644/36, April 27,2018)**

*Bio Products Laboratory Inc. commits to perform method validation for the determination of (b) (4) concentration for intermediate precision using well characterized standards to establish a 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.*

*Final Report Submission: December 19, 2018*

**Executive Summary:**

STN 125644 is an original biologics license application (BLA) submitted by Bio Products Laboratory for Albumin (Human). 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. Only (b) (4) plasma from FDA-licensed collection centers are used in the manufacture of Albuminex®. BPL also manufactures Albumin (Human) primarily for marketing in the United Kingdom at 45 g/L and 200 g/L under the trade name Zenalb®.

Primary indications for use of Albumin (Human) include hypovolemic shock, burns, pancreatitis and peritonitis, Adult Respiratory Distress Syndrome (ARDS), priming as part of cardio bypass pulmonary procedures, pre – and postoperative hypoproteinemia (b) (4) acute liver failure, acute nephrosis, ascites, and renal dialysis.

STN 125644 was reviewed under the standard schedule of PDUFA V. The package was received on Dec 6, 2016. FDA issued a Complete Response (CR) letter that was transmitted on August 25, 2017. The letter listed 28 items from CMC product (8 items), DMPQ (19 items) and labeling (1 item). Prior to the issuance of the CR letter, BPL had submitted 28 amendments addressing a variety of Information Requests related to issues from CMC, Pharm/Tox, labeling, method validations, and manufacturing.

FDA received a response to the CR letter on Dec. 19, 2017. The response was classified as a class 2 resubmission.

Within the scope of this review are CMC issues related to 3.2.S.2 Manufacture, Control of Drug Substance, Reference Standards or Materials, Description and Composition of the Drug Product, Pharmaceutical Development, Manufacturer, Excipient Specifications, Analytical Procedures, and In-process controls.

Substantive CMC issues resolved during the review include method validations for (b) (4) testing, viral clearance, and (b) (4).

Approval is recommended based on information within the scope of this review with the following post-marketing commitment, agreed to by the sponsor as part of amendment 125644/36 on April, 27, 2018.

*Bio Products Laboratory Inc. 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.*

*Final Report Submission: December 19, 2018*

**Background:** Human Serum 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 helps maintain oncotic pressure. Albumin also serves as transport protein for various fatty acids, growth factors, fatty acids, chaperones, metal ions, and toxic substances. Albumin (Human) has a molecular weight of ~66,000 kDa and contains 609 amino acids prior to processing of the signal peptide, amino acids (a.a) 1 – 18 and the propeptide amino acids 19 - 24. Mature albumin contains 585 amino acids. Albumin contains 17 disulfide bridges which play a key role in the structure, function and stability of the protein. Albumin has three domains, domain I from a.a. 19- 210, domain II from a.a. 211 – 403, and domain III from 404 – 601. Normal concentration of Albumin in blood is ~ 35 – 50 g/L. In addition to its use as a colloid replacement, Albumin is now used as an excipient and as to increase the half- life of other therapeutics.

Albumin can undergo glycation and oxidation reactions. These modifications are non-uniform and are a source of heterogeneity of plasma-derived albumin.

Albumin (Human) can be produced by recombinant methods, however it is more commonly purified from blood plasma. Purification of Albumin from blood plasma is generally done by two different fractionation methods, and variations thereof. The oldest method, the Cohn method was developed in the 1940s for the separation of Albumin. This process uses the approach of

(b) (4)

Albumin. Other blood products, such as coagulation factors, immunoglobulins, and Alpha1PI are also produced upstream of albumin by this process. Albumin is produced from fraction V.

The Kistler-Nitschman fractionation process is a variation of the Cohn process which reduces the volumes and amount of ethanol used by eliminating fraction IV. Methods that make use of chromatographic columns as opposed to centrifugation are also utilized. The process has a lot of variants and is dependent on the manufacturer's production of other blood products.

Bio Products Laboratory (BPL) was established as part of Lister Institute in 1950, as part of the Medical Research Council for the processing of Human plasma. BPL was purchased by Bain Capital in 2013 and more recently by Creat, a Chinese Investment group. BPL manufactures

Coagulation factors for Hemophilia A under the name Optivate ®, Coagulation factors for Hemophilia B under the name Replenine ®. BPL also produces Normal immunoglobulins and specific immunoglobulins.

Submission Received:

STN: 125644

Sponsor: Bio Products Laboratory

Submission type: Biological License Application

Manufacturing Facility: Dagger Lane

Elstree, Hertfordshire WD63BX

United Kingdom

Contracting Lab for Adventitious Agent Testing:

(b) (4) [Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]

Contract sites for NAT testing of (b) (4) [Redacted]

(b) (4) [Redacted]  
[Redacted]  
[Redacted]

(b) (4) [Redacted]  
[Redacted]  
[Redacted]  
[Redacted]

(b) (4) [Redacted]  
[Redacted]  
[Redacted]

(b) (4) [Redacted]  
[Redacted]  
[Redacted]

(b) (4) [Redacted]  
[Redacted]  
[Redacted]

**Sections Reviewed Herein:**

3.2.S.2 Manufacture

3.2.S.4 Control of Drug Substance

3.2.S.5 Reference Standards or Materials

3.2.P.1 Description and Composition of the Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.3 Manufacturer

3.2.P.4.1 Excipient Specifications

3.2.P.4.2 Analytical Procedures

3.2.P.6 Reference standards or Materials

3.2.P.7 Container Closure System

**Chemistry, Manufacturing and Controls (CMC) Sections Reviewed by Other Reviewers:**

Michael Strader: (Drug Substance and Drug Product Characterization and Stability)

Drug Substance Characterization:

3.2.S.2 Manufacture

3.2.S.2.6 Manufacturing Process Development

3.2.S.3 Drug Substance Characterization

3.2.S.4.4 Batch Analysis

3.2.S.6 Container Closure System

3.2.P.1 Description and Composition of the Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.4 Control of Excipient

3.2.3.P.5 Process Validation and/or Evaluation

3.2.P.8 Stability

Tigist Kassa: (Analytical Procedures and Method Validation)

3.2.S.4. Validation of Analytical Procedures

3.2.S.4.2 Analytical Procedures

3.2.P.2 Pharmaceutical Development

3.2.S.3 Manufacture

3.2.P.3.5 Control of Drug Product

**Table 1 Composition of Albumin (Human) 5% and 25%**

Composition	Albumin (Human) 5%	Albumin (Human) 25%
Active		
Albumin (Human)	(b) (4)	
Excipients		
Sodium	130 – 160 mmol/L	130 – 160 mmol/L
(b) (4)-Acetyl-(b) (4)-Tryptophan, (b) (4)	(b) (4)	
Caprylic Acid, (b) (4)		
(b) (4)		

Note: (b) (4)  
(b) (4) (2) Sodium Hydroxide or (b) (4) is added as required to adjust pH.

**Complete Response Items:**

**FDA sent the following comments to the sponsor:**

1) Regarding the information provided for determination of accuracy for the (b) (4) testing method described in section 2.4.2 of module 3.2.S.4.

Results of this testing show that the acceptance criterion for sample (b) (4) was not met. The sponsor stated in their response received on May 26, 2017 (STN 125644/0.15) that there are no comparable samples currently available to provide the additional data.

BPL commits to performing additional work when the manufacture of the product is scheduled and samples become available. Please note that the unspiked (b) (4) concentrations are dependent on the process for each batch, and as such (b) (4) concentrations of exactly (b) (4) cannot be guaranteed. Please provide proper validation data for this method prior to approval.

2) Regarding the evaluation of (b) (4) testing in section 3.2.S.2.6.of the (b) (4) for production batches (b) (4) an expired (b) (4) was used for an (b) (4) assay for (b) (4) during the validation testing of the (b) (4) step. Please validate this assay using non-expired materials.

3) Regarding the information provided for viral clearance submitted on May 26, 2017 under STN 125644/0.15. The information provided did not establish viral clearance for HIV virus using at least two major and independent viral clearance steps where each clearance step provides > 4 logs of clearance. The cumulative log reduction for a given virus is recommended to be greater than 10 logs. In your submission, HIV inactivation by heat treatment has been validated, however, no studies were performed to validate HIV removal by the (b) (4) steps. BPL

indicated that they can provide FDA with this confirmatory information no later than end Q2 2018. Please submit complete viral clearance data for the HIV virus.

4) Regarding the information provided on May 26, 2017, STN 125644/0.15 for module 3.2.S.4 method for (b) (4) determination.

a. The results of the repeatability studies for validation of (b) (4) failed according to the sponsor's own established standards. Please submit validation data that demonstrate the repeatability of (b) (4) determination.

b. The results of the intermediate precision studies for validation of (b) (4) failed according to the sponsor's own established standards. Please submit intermediate precision data repeatability of (b) (4) determination.

c. An inadequate number of samples were used in the the accuracy studies for validation of (b) (4) . The sponsor committed to provide new data with the appropriate number of samples no later than July 21. As of July 23, 2017, this data has not been received. Please provide the requested data included in the accuracy studies for validation of (b) (4) .

### **3.2.S.2 Manufacturing:**

Bio Products Laboratory manufactures HSA at two concentrations, 5% and 25%. HSA is manufactured using from (b) (4) plasma collected from FDA inspected collection centers located in the United States.

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



**Bulk Drug Substance**

(b) (4)



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

**3.2.S.2.2 S (1.3) Description of Drug Substance Manufacturing Process**

(b) (4)

[Redacted text block containing multiple lines of obscured content]



(b) (4)

(b) (4)

(b) (4)

**Sect. 3.2.P.3.2 Batch Formula:**

Typical Batch size for HSA 25% is given in the table below.

Batch Formula for typical HSA 25%

(b) (4)



(b) (4)

(b) (4)

**(Sect. 3.2.A.2) Adventitious agents:**

(b) (4)

The removal of adventitious agents during manufacture of HSA includes Scrapie, which is also referred to as Creutzfeld-Jakob Disease (CJD), variant CJD and Transmissible Spongiform Encephalopathy. Manufacturing processes have been assessed for their ability to remove prion based agents.

Start Materials:

(b) (4)

(b) (4)

(b) (4)





**Sect. 3.2.A.2.2.1 Adventitious Viruses Approach to Virus Safety**

The sponsors main strategy for controlling viral contamination are donor screening, testing of the plasma and viral reduction steps in the manufacturing process. The major manufacturing viral reduction step considered is Pasteurization at 60 °C. (b) (4) fractionation is also considered to contribute to viral reduction.

**Table 1 Main Viruses Potentially Transmitted by Plasma Products**

<b>Virus</b>	<b>Family</b>	<b>Genome</b>	<b>Envelope</b>	<b>Size (nm)</b>	<b>Shape</b>
HIV-1/-2 HTLV-1/-2	Retro	RNA	+	80-100	Spherical
HBV	Hepadna	DNA	+	40-45	Spherical
HCV HGV/GBV-C WNV	Flavi	RNA	+	40-60	Spherical
HAV	Picorna	RNA	-	30	Icosahedral
B19	Parvo	DNA	-	18-26	Icosahedral

HIV-1/-2: human immunodeficiency virus type -1/-2  
 HTLV-1/-2: human T-cell leukaemia virus type -1/-2  
 HBV: hepatitis B virus  
 HCV: hepatitis C virus  
 HGV: hepatitis G virus or HGV-C: GB virus C  
 WNV: West Nile virus  
 HAV: hepatitis A virus  
 B19: human parvovirus B19

Sect. 3.2.A.2.2.2 Biological Materials Used in Production:

(b) (4) [Redacted]



**Table 2 Principle Factors that Contribute to Virus Safety**

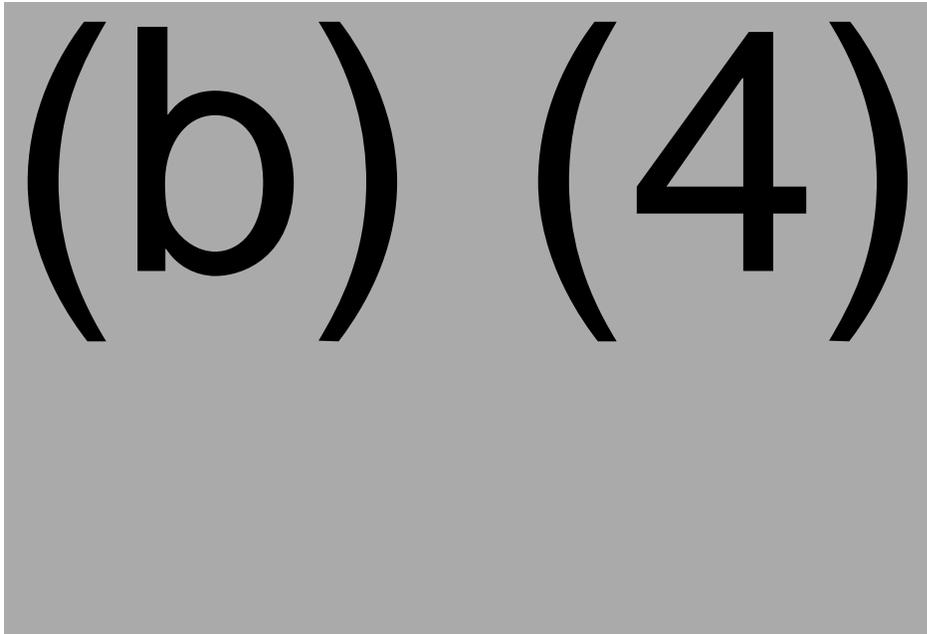
Stage	Virus reduction	
	Enveloped Virus	Non-Enveloped Virus
Donor Medical Assessment	Yes	Yes
Viral Marker Testing of each Donation	Yes	No
NAT Testing of (b) (4)	Yes	Yes
Inventory Hold	Yes	Yes
NAT Testing of (b) (4)	Yes	Yes
(b) (4)	Yes	Yes
	Yes	Yes
Terminal pasteurisation at 60°C for (b) (4)	Yes	Yes
GMP Compliance	Yes	Yes
Advice to Clinicians	Yes	Yes

Sect. 2.3.2 Validation methods:

Validation of viral removal methods during manufacturing is reported to follow recommendations as outlined by EMA (CHMP, 2010: CPMP 1996) and WHO 2004. The sponsors also indicate that it follows relevant aspects of ICH Q5 A.

Sect. 2.3.3 Virus Models used in Validation studies:

Viruses listed in the following tables were used in the validation studies.



(b) (4)

Sect. 2.5.7 Virus Inactivation:

The following tables indicate viral inactivation at each relevant manufacturing step using a small-scale model.

**a) Enveloped Viruses**

Step	Reduction (log <sub>10</sub> )			
	HIV-1	Sindbis	BVDV	IBR
<b>A+1 Precipitation<sup>[G]</sup></b>	nd	4.1 <sup>[B]</sup>	>3.4 <sup>[C]</sup>	3.4 <sup>[B]</sup>
<b>Fraction IV Precipitation</b>	nd	>7.1 <sup>[D]</sup>	>4.2 <sup>[D]</sup>	>5.7 <sup>[D]</sup>
<b>Pasteurisation<sub>(b) (4)</sub></b>	>6.7 <sup>[E]</sup>	>6.4 <sup>[F]</sup>	>4.2 <sup>[F]</sup>	>5.4 <sup>[F]</sup>
<b>Total</b>	>6.7 <sup>[A]</sup>	>13.5	>8.4	>11.1

nd, not determined.

<sup>[A]</sup> When minimum estimates for A+1 and Fraction IV for other model enveloped viruses a total of [redacted] log

<sup>[B]</sup> Data from Appendix 3.2.A.2.2 -3

<sup>[C]</sup> Data from Appendix 3.2.A.2.2 -2

<sup>[D]</sup> Data from Appendix 3.2.A.2.2 -6

<sup>[E]</sup> Data from Appendix 3.2.A.2.2 -10

<sup>[F]</sup> Data from Appendix 3.2.A.2.2 -9

<sup>[G]</sup> Step not included in the total

## b) Non-Enveloped Viruses

Step	Reduction (log <sub>10</sub> )	
	HAV	CPV
<b>A+1 Precipitation<sup>[D]</sup></b>	3.4 <sup>[A]</sup>	3.7 <sup>[A]</sup>
<b>Fraction IV Precipitation</b>	4.2 <sup>[B]</sup>	6.0 <sup>[B]</sup>
<b>Pasteurisation</b>	4.0 <sup>[C]</sup>	4.0 <sup>[C]</sup>
<b>Total</b>	8.2	10.0

nd, not determined.

<sup>[A]</sup> Data from Appendix 3.2.A.2.2 -3

<sup>[B]</sup> Data from Appendix 3.2.A.2.2 -6

<sup>[C]</sup> Data from Appendix 3.2.A.2.2 -9

<sup>[D]</sup> Step not included in the total

Virus reduction summary for Albumin 25%.

**Table 6 Virus Reduction Summary: 25% Human Albumin**

### a) Enveloped Viruses

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

nd, not determined.

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

<sup>[B]</sup> Data from Appendix 3.2.A.2.2-3

<sup>[C]</sup> Data from Appendix 3.2.A.2.2-2

<sup>[D]</sup> Data from Appendix 3.2.A.2.2-6

<sup>[E]</sup> Data from Appendix 3.2.A.2.2-11

<sup>[F]</sup> Data from Appendix 3.2.A.2.2-9

<sup>[G]</sup> Step not included in the total

**b) Non-Enveloped Viruses**

Step	Reduction (log <sub>10</sub> )	
	HAV	CPV
<b>A+1 Precipitation<sup>[D]</sup></b>	3.4 <sup>[A]</sup>	3.7 <sup>[A]</sup>
<b>Fraction IV Precipitation</b>	4.2 <sup>[B]</sup>	6.0 <sup>[B]</sup>
<b>Pasteurisation</b>	4.7 <sup>[C]</sup>	4.2 <sup>[C]</sup>
<b>Total</b>	8.9	10.2

nd, not determined.

<sup>[A]</sup> Data from Appendix 3.2.A.2.2 -3

<sup>[B]</sup> Data from Appendix 3.2.A.2.2 -6

<sup>[C]</sup> Data from Appendix 3.2.A.2.2 -9

<sup>[D]</sup> Step not included in the total

Only the Pasteurization step reflects virus inactivation conditions that include (b) (4) concentrations present in the finished product.

Appendix 10 Validation of the Inactivation of human immunodeficiency virus by Pasteurization in the manufacturing process of 5% Albumin:

(b) (4)

[Redacted]

[Redacted]

[Redacted]



**Sect. 3.2.P.3.3 Description of Manufacturing Process and Process Controls**

(b) (4)

1.3 Description of HSA 5% and 25% Manufacturing Process:

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]



### 3.2.P.5.1 Drug Product Specifications

**Table 2 HAS 5% and 25 % Labelled Product Specification Tests**

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

NLT Not Less Than

#### Summary of questions, responses and comments.

#### **Questions: Submitted on March 6, 2017**

##### Reviewer's Question:

1) Was the equipment used for (b) (4) manufacture previously used to manufacture of Albumin lots?

##### Sponsor's Response:

**Yes, the equipment used for (b) (4) manufacture is also used to manufacture other Albumin (i.e. Zenalb® registered in the UK) with the exception of the following equipment;**

(b) (4)

**These two pieces of equipment will be used for the (b) (4) BPL acknowledges for not having responded to the March 6th 2017 Information request, however the question was responded to as part of the deficiency letter (08th February 2017). The answer to this question was provided to the FDA on the 26th April 2017 under Question 14 under Equipment, part i.**

##### Reviewer's Comment:

The sponsor's response is acceptable regarding the shared use of equipment; however, the sponsor did not respond directly to the information request that was submitted until June 23, 2017.

##### Reviewer's Question:

2) Please submit validation data for all equipment used to include heat pasteurization, filling apparatus (b) (4).

##### Sponsor's Response:

**The sponsor provided a lengthy response to the above information request. BPL acknowledges for not having responded to the March 6th 2017 information request, however the question was responded to as part of the deficiency letter (08th February 2017). The answer to this question was provided to the FDA on the 28th April 2017 under Question 3, part i.**

Reviewer's Comment:

The sponsor did not respond directly to the information request that was submitted until June 26, 2017. The sponsor did provide this data as part of their resubmission package received on December 18, 2017. Please see page 44, in the section on viral clearance for a summary of the information provided by the sponsor.

Reviewer's Question:

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.

Sponsor's Response:

**BPL acknowledges for not having responded to the March 6th 2017 Information request, however the sponsor's response to this question was submitted as part of a previous IR response (18th January 2017).**

Reviewer's Comment:

The sponsor's response was acceptable with regards to content; however, the sponsor did not respond directly to the information request that was submitted until June 26, 2017. The sponsor's response was reviewed as part of their resubmission package.

Reviewer's Question:

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.

Sponsor's Response:

**A table and manufacturing flow diagram that outlines each manufacturing step and the equipment associated with each step and its location in manufacturing site is presented in the following**

- 1. in Table for Equipment and manufacturing Steps (Appendix 21)**
- 2. Human Albumin Solution 5% and 25% flow diagram (Appendix 22)**
- 3. List of Equipment for Human Albumin Solution 5% and 255 Manufacturing (Appendix 23).**

**BPL acknowledges for not having responded to the March 6th 2017 Information request, however the question was responded to as part of a previous IR (18th January 2017).**

**The answer to this question was provided to the FDA on the 24th January under Question 1. The answer was then further responded to as part of the deficiency letter (08th February 2017). The response can be found in Question 14 (Equipment) part I.**

Reviewer's Comment:

The sponsor's response was acceptable with regards to content; however, the sponsor did not respond directly to the information request that was submitted until June 23, 2017. The sponsor's response is acceptable following resubmission.

Reviewer's Question:

5) Please submit a table showing all in-process controls associated and the manufacturing step with which it is associated.

**Sponsor's Response:**

**A response was provided for this question on June 26, 2017.**

Reviewer's Comment:

It was pointed out during the mid-cycle teleconference with the sponsor on June 14, 2017 that a response had not been provided. A response was submitted on June 26, 2017; however, the late response was not sufficient for complete review. The response submitted by the sponsor indicated that sampling was done during filling however the table provided appears incomplete, e.g. The original submission indicated that (b) (4) is tested at multiple sampling points however the table indicates only a single manufacturing step when (b) (4) testing is done.

Reviewer's Question:

6) Please submit complete batch records for all conformance lots.

**Sponsor's Response:**

**BPL acknowledges for not having responded to the March 6th 2017 Information.**

**The 1st batch record was included in the submission as part of the original submission (December 09 2016) in Regional Information (3.2.R) sequence 0000.**

**The 2nd batch was provided in response (29th Mach 2017) in response to the deficiency letter dated 08<sup>th</sup> February 2017. The response was outlined in Question 11 in Regional Information (3.2.R) sequence 0003.**

Reviewer's Question:

7) Please submit a report listing all deviations and out of specification results that occurred during validation studies for (b) (4) 5% and 25%.

**Sponsor's Response:**

**The sponsor provided a table listing of specification results as a response.**

Reviewer's Comment:

A response was provided; however, this response was not received until July 7, 2017. It was agreed during the telecom that the sponsor would submit a schedule for response to outstanding information requests one week from the date of the mid-cycle teleconference between FDA and Bio Products Laboratory no later than June 21, 2017. The agreed upon schedule was not submitted until June 23, 2017. That schedule indicated that the response to the above question 6

would be submitted on June 26. However, that document indicated that a response to the above question would not arrive until July 7, 2017.

The information that finally was submitted on July 7 contained an extensive table of out of specification results that are too numerous to be adequately reviewed with the original review clock. Some of the items of concern are quality record 96253, Over action (b) (4) sample for (b) (4) sample for (b) (4) rinse, 96268 Over Action (b) (4) sample action limit for (b) (4) sample associated with (b) (4) line, 96409 QC (method validation) atypical appearance of material requested for method validation, 96543 Total protein result for stage (b) (4) was out of specification, 96696 (b) (4). (b) (4), 96713 (Thermostability test) specification was not met due to the appearance of several (b) (4) in the thermostability (b) (4), 98514 QACoo321 determination of total (b) (4) protein by (b) (4) method.

### **Questions submitted as of May 12, 2017:**

#### **Reviewer's Question:**

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.

#### **Sponsor's Response:**

**The requested information was provided.**

#### **Reviewer's Comment:**

The sponsor provided a response that was received beyond the agreed upon date. The response was received on June-23-2017. However, a schedule indicating when the response was to be submitted was two days late. The sponsor's response was reviewed following the issuance of a CR letter and resubmission and found to be acceptable.

#### **Reviewer's Question:**

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

#### **Sponsor's Response (received 6/23/2017, STN 125644/0.18) :**

**The sponsor acknowledged that the response to this question was not included with the responses to other information requests that were also submitted on May 12, 2017. The sponsor provided a response that included the above requested information as part of**

SOPP QAC00321 and validation protocol LP/805/1/04/01. SOPPQAC00321 and validation protocol LP/805/1/04/01 were included with the sponsors response.



b) Human Albumin Solution 5% and 25% intermediate stage code (b) (4) which were the same samples as in section 3.2.S.4.4 batch analysis Table 1 and 2. The preparation method is as per SOP QAC00321 and validation protocol LP/805/1/04/01 (see Appendix 1).

c) The statistical calculation of error (%RSD or CV) in measurement for replicates samples are provided below for each study.

The accuracy measurement gave a recovery results of (b) (4) with (b) (4). This result is not in agreement with the acceptance criteria of (b) (4), however this is due to one sample (b) (4).

The repeatability measurement gave a %RSD of (b) (4).

The intermediate precision measurement gave a %RSD of (b) (4).

The linearity and range measurement gave a %RSD of (b) (4).

The robustness measurement gave a %RSD of (b) (4). (Incorrect batch number in CTD –

This will be updated with correct batch number)

Validation Protocol, Validation Report and Method summary are also provided to assist with the review (Appendix 2).

*Reviewer's Comment:*

The sponsor's response is acceptable in content however a schedule that indicated the expected date for responses to outstanding IRs which included this item was submitted two days beyond the agreed upon date, review of this matter is still ongoing.

The above reported results are acceptable. Regarding the OOS results for accuracy; the sponsor tested the sample at other concentration of (b) (4) spikes and unspiked and obtained results

consistent with specifications. The single OOS result can be an outlier and not impactful to the validity of the method. The sponsor's response is acceptable. It appears that one sample was used for robustness measurements and only a single measurement was made for each parameter.

Reviewer's Question:

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.

**Sponsor's Response:**

**The reference standard used is (b) (4) Standards, Catalogue No. (b) (4) bottles, one each of (b) (4). The standard is (b) (4) according to the assay procedure to cover the concentration range (b) (4).**

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

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

**Sponsor's Response:**

(b) (4)

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

12) 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 (b) (4) and two additional samples with unspiked (b) (4) concentrations of (b) (4) respectively.

**Sponsor's Response:**

**At present, there are no comparable samples currently available to provide the additional data. BPL commits to performing additional work when the manufacture of the product is scheduled and samples become available. Please note that the unspiked (b) (4) concentrations are dependent on the process for each batch, and as such (b) (4) concentrations of exactly (b) (4) cannot be guaranteed.**

**Reviewer's Comment:**

The sponsor's response is not acceptable. All methods should be validated prior to BLA submission. All acceptance criteria should be met. Sample concentration should be sufficient for detection by the method of choice, or modifications of the method itself or the testing protocol should be made. (CR comment item 1)

**Sponsor's Response from the resubmission received on 12/18/2017:**

BPL revalidated the method for accuracy and precision using in-process intermediates (b) (4) final product samples. The following table summarizes the results. Validation protocols and reports were also provided for both intermediates and final product.

(b) (4)

**Reviewer's Comment:**

The sponsor's response is acceptable.

**Reviewer's Question:**

13) 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

**Sponsor's Response:**

**a) (b) (4) assay by (b) (4) was used. (b) (4) is determined by (b) (4) using an internal standard method. The internal standard used is (b) (4). Refer to SOP QAC00308 attached.**

**b) The values were calculated using a standard calibration curve generated as per section 11 of the assay procedure SOP QAC00308.**

**c) The original results are reported below:**

(b) (4)

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

14) 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.

**Sponsor's Response:**

(b) (4)

[Redacted]

Reviewer's Comment:

The sponsor's response is acceptable for content; however, the raw data should have been included in the original BLA as recommended by the FDA Guidance for industry for BLA submission.

Reviewer's Question:

15) 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.

**Sponsor's Response:**

(b) (4)

[Redacted]



(b) (4)

Reviewer Comment:

The sponsor's response is acceptable.

Reviewer Question:

16) The data provided in table 15 of section 2.4.2 of module 3.2.S.2.4 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?

Sponsors Response:

Concentration levels (b) (4) were also tested on the final products. Table of results for the final product is shown below.

(b) (4)

a. The lower and upper limit of detection for this method is (b) (4) respectively.

**b. The linear range of the method is (b) (4) according to section 4.4 of SOP QAC00308.**

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

17) Please explain why batch (b) (4) 5% HSA is out of compliance for visual inspection and submit any out of specification reports and deviation investigations?

Sponsor's Response:

**During inspection of (b) (4) were observed to contain (b) (4). This breached the limit of (b) (4). BPL understands that the occurrence of (b) (4) is not uncommon in liquid filling operations within the industry and is not specifically related to the HAS 5% product. Occasional spikes in the incidence of (b) (4) can occur and it is difficult to definitively identify a single root cause. This has been investigated by a high level of scrutiny of the process operation and comparison to a library of test results using (b) (4) allowing identification of (b) (4). In this case the (b) (4) was identified as (b) (4). The inspection methods and pass criteria ensure the quality of the product. The Quality Report (QR 96853), see Appendix 1 raised as a result of the over limits inspection is attached along with the inspection Batch Processing Record entitled (b) (4) Filling Records (see Appendix 2) and also the investigation report (Appendix3).**

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

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

Sponsor's Response:

**The performance qualification lots of HAS 5% and HAS 25% were manufactured consecutively. No additional batches of HAS 5% or HAS 25% were manufactured at BPL over the time period shown in Table 1 or subsequently. A development batch was manufactured prior to qualification in December 2015. As BPL is a multi-product facility the batch numbering of the Performance Qualification lots is not consecutive as this reflects unique numbers used in the common upstream parts of the process as well as entirely unique numbers used for coding all final products. Human Albumin Solution batches were made in between routine processing of other products including batches of Zenalb and Gammalex for which the unique number coding system also applies.**

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

19) 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.

Sponsor's Response:

The (b) (4) Method is a (b) (4) assay whereby (b) (4)

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

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

Sponsor's Response:

(b) (4) is defined as the reportable (b) (4) not greater (b) (4) . Whilst the finished product specification (3.2.P.5.1) states for (b) (4) it is BPL intention to report (b) (4) since the emphasis is on the % protein composition of Albumin. BPL proposes to update the finished product specification (3.2.P.5.1), by removing the word "(b) (4)".

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

21) "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. Thus, 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.

Sponsor's Response:

HIV studies were not performed based on a scientific assessment of the data from studies of the BPL process using model viruses in combination with the published evidence and long term safety record of both BPL's and other manufacturer's albumin products. The data on

other more resistant viruses presented in section 3.2.A.2 of the BLA was considered sufficient to establish product safety. This is in addition to the long established safety record of BPL's albumin products, which are made using the same (b) (4) fractionation process. Furthermore, BPL were not aware of any US regulation or guidance document requiring or recommending that such studies be done with HIV when the plethora of data support the viral safety of the product. The viral safety of Albumin is assured at a number of levels as described below. The donors used for producing Albumin reside in the United States (US) and are required to meet specific donor health criteria before selection, as determined by medical assessment. The Collection centres are licensed and inspected by the FDA. Donors must be negative for various viral markers, i.e. HBsAg, anti- HIV-1/2, anti-HCV, on two consecutive occasions using FDA approved test kits. In addition, testing for these viral markers is carried out on each plasma donation. The results are further confirmed by testing plasma (b) (4)

Each donation is quarantined before use thus enabling any donations from a donor that subsequently turns positive, to be identified and removed. In conclusion, the extensive testing reduces the viral risk for a wide range of viruses including HIV. The classic (b) (4) process, combined with terminal heat treatment (pasteurisation) at 60°C for 10 hr, has a long history of producing virus safe albumin products since World War II (WWII) (EMA/CHMP/BWP/706271/2010). Various steps in the (b) (4) process itself, contribute to virus reduction by removing virus into the (b) (4) (combined with virus inactivation in some cases where (b) (4) is involved). This has proven to be consistently effective for a wide range of viruses including HIV, and a range of products (see Appendix 1 for (b) (4)).

The (b) (4) step has also been investigated to confirm its contribution to virus reduction for BPL's Albumin products (Table 1). The A+1 precipitation step at (b) (4) (b) (4), was shown to give reduction values of 3.4-4.1 log for a range of model enveloped viruses, representative of HIV (Table 1). In addition, non-enveloped viruses, which are generally more resistant, were also tested. In the case of the Fraction IV step, which involves precipitation at a (b) (4), a reduction value of at least 4.0 log was demonstrated for a range of enveloped viruses representative of HIV, with a value of up to >7.1 log for Sindbis. Some of the viruses tested are considered particularly resistant to virus reduction procedures e.g. IBR (a herpes virus equivalent to Pseudorabies) is of medium resistance and (b) (4)/CPV (CPMP/BWP/268/95) is of high resistance. This compares with HIV which is considered to be of relatively low resistance. In addition, the robustness of virus reduction with regard to a number of process variables has been confirmed for this process with a range of virus models similar to HIV (Table 2). Based on the lowest worst-case reduction value demonstrated for a range of model enveloped viruses ((b) (4) log), the total reduction for HIV can be estimated to be (b) (4) log.

*Reviewer's Comment:*

The sponsor's response is not acceptable. Please note that viral validation data must be virus and process specific. Therefore, extrapolating the level of clearance for HIV at the precipitation steps based on data obtained for other viruses would not be acceptable. We encourage you to generate specific validation data, pre-approval, for HIV clearance at precipitation steps to provide a margin safety for this virus that would be comparable to that currently available for Albumin products marketed in the U.S. Please refer to ICH 5 A (R1) section C (vii). (CR comment 3)

**Sponsor's Response to CR Letter (December 18, 2017)**

**Further HIV virus clearance data has now been obtained for Albumin for the fraction IV precipitation step (see (b) (4) Report). In this case the virus reduction value was >4.6 log. With this data, both virus reduction steps have been shown to give values of >4 log and a cumulative total of >10 log (Table 1). (The table below that quantitates viral clearance of individual steps and total viral reduction (Table 2).**

**Table 2 Virus Reduction in Human Albumin:**

	HIV-1 Reduction (log <sub>10</sub> )	
	5%	25%
<b>Fraction IV Precipitation<sup>[A]</sup></b>	>4.6	>4.6
<b>Pasteurisation<sup>[B]</sup></b>	>6.7	>6.6
<b>Total</b>	>11.3	>11.2

<sup>[A]</sup> Data from report K1/B33/17 attached

<sup>[B]</sup> Data from Appendix 3.2.A.2.2

*Reviewer's Comment: Acceptable*

The sponsor's response is acceptable.

Reviewer's Question:

22) 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) ?

**Sponsor's Response:**

The (b) (4) process used in the manufacture of Human Albumin Solution is a preparative method and the (b) (4) are not necessary to achieve the (b) (4) required from this step. As such the system suitability tests typically associated with analytical (b) (4) methods have not been applied to the system. The step has been validated as described in 3.2.S.2.5.5 and this includes the details of the (b) (4) measurements taken following the (b) (4) . These details are shown below in Table 1. The (b) (4) are used as a means of establishing the

suitability of the (b) (4) , in conjunction with the process control system to achieve the required performance.

(b) (4)

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

23) 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.

Sponsor's Response:

The requested information was provided by the sponsor in amendment 125644/0/18 received on June 23, 2017.

Reviewer's Comment:

The sponsor's response is acceptable.

Reviewer's Question:

24) 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.

Sponsor's Response:

(b) (4) batches of Human Albumin Solution 5% and 25% intermediate stage code (b) (4) were used for the accuracy test and (b) (4) batches of final product were also used in another laboratory protocol (LP/805/1/12/01) under the same project; total of (b) (4) samples used. The data in Table 19 is for the (b) (4) intermediate samples only. The data for the (b) (4) final product samples is in the drug product section (cross ref). The accuracy test was determined by the recovery of known amounts of (b) (4) (reference standard) added to the samples at different concentration levels. (b) (4) determinations each for (b) (4) samples ((b) (4) intermediates and (b) (4) final products) were tested at (b) (4) different (b) (4) concentration levels ((b) (4) ) across the range of the assay in

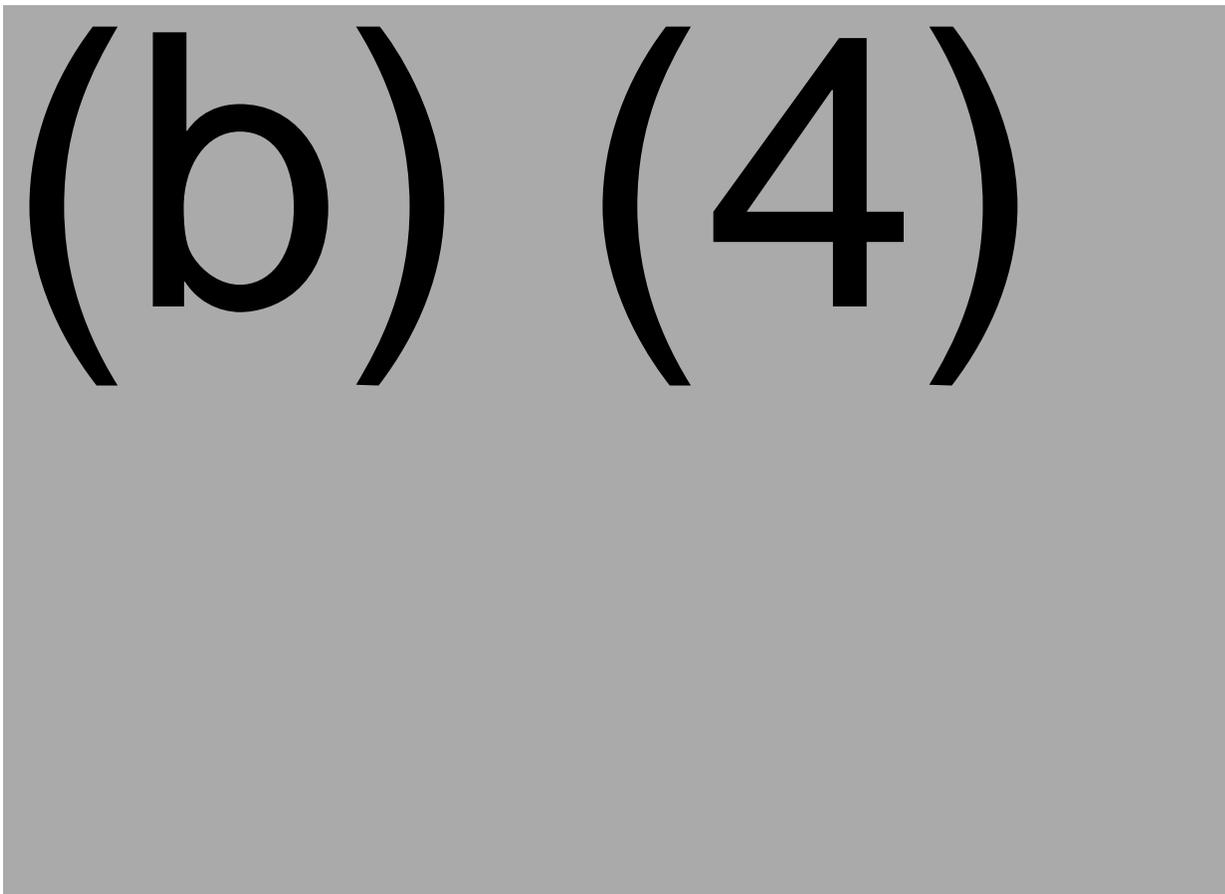
accordance with ICH Q2 (R1). The samples were prepared as per section 10 of the SOP QAC00402 and the standard additions were (b) (4) standard as per the laboratory protocol LP/805/2/12/01. There was no positive and negative control used as a reference standard was used. The data reported in table 19 are the raw data with the (b) (4) calculated as (b) (4). Acknowledging that the (b) (4) assay is an in-process test, BPL will repeat the accuracy using the appropriate number of intermediate batches. The data from this additional work will be provided by 21<sup>st</sup> July 2017.

Reviewer's Comment:

The sponsor committed to providing data from a repeat of the accuracy testing no later than July 21, 2017. As of July 23, 2017 this information was not provided. (CR item 6)

Sponsor's Response: (Submitted 12/18/2017)

The sponsor submitted data from an additional (b) (4) samples the data appears in the table below. The samples used were in-process intermediates



Reviewer's Comment

The reported results are within the acceptance criteria established by the sponsor. The response is considered acceptable.

Reviewer's Question:

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 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)

Sponsor's Response:

(b) (4) batches of Human Albumin Solution 5% and 25% intermediate stage code (b) (4) were used for the repeatability test and (b) (4) batches of final product (batch number (b) (4)); total of (b) (4) samples used. The samples were prepared as per section 10 of the SOP QAC00402. (b) (4) determinations each for (b) (4) samples ((b) (4) intermediates and (b) (4) final products) were tested at (b) (4) of the sample concentration in accordance with ICH Q2 (R1). The data in Table 20 is for the (b) (4) intermediate samples only. The data for the (b) (4) final product samples tested is shown below. The acceptance criterion of an RSD of (b) (4) was not met as the amount of (b) (4) in the sample was close to the detection limit of (b) (4). The RSD criterion is a statistical calculation used to assess the assay variability and has no quality impact on the samples tested. The amount of (b) (4) expected in the sample is very low with a specification limit of (b) (4) and thus a (b) (4) RSD is expected. All (b) (4) determinations for each sample gave consistent results of (b) (4); an indication that the method is precise for determination of (b) (4). Hence the RSD failure is considered not significant as it has no quality risk on the product nor the sample tested. ICH Q2 (R1) requires a minimum of six determinations at 100% the sample concentration, a total of (b) (4) samples with (b) (4) determinations each were tested in this study.

(b) (4)

Reviewer's Comment:

The sponsor's response is not acceptable. (CR comment 4)

Sponsor's Response: (12/18/2017)

Repeatability measurements were redone using the same in-process samples that were used for the accuracy studies. This validation failed as results obtained for (b) (4) of the samples

were outside of specification for RSD. The sponsor's explanation is essentially the same as that previously given that the samples are at or near the detection limit.

Reviewer's Comment:

The sponsor needs to establish a valid range for their assay in which reproducible results are obtained. A post-marketing commitment was agreed upon to revalidate the (b) (4) assay for precision, linearity, range, and repeatability.

Reviewer's Question:

28) In section 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.

Sponsor's Response:

The acceptance criterion of an RSD of (b) (4) was not met as the amount of (b) (4) in the samples was close to the detection limit of (b) (4). The RSD criterion is a statistical calculation used to assess the assay variability and has no quality impact on the samples tested. The amount of (b) (4) expected in the sample is very low with a specification limit of (b) (4) and thus a (b) (4) RSD is expected. All (b) (4) determinations for each sample gave consistent results of (b) (4); an indication that the method is precise for determination of (b) (4). Hence the RSD failure is considered not significant as it has no quality risk on the product nor the sample tested. The data in Table 21 is for the (b) (4) intermediate samples only. The data for the (b) (4) final product samples tested by (b) (4) different Analysts over a (b) (4) period is shown below.

(b) (4)

Reviewer's Comment:

The sponsor's response is not acceptable. This was listed as CR comment 5 in FDA's complete response letter issued on August 25, 2017.

Reviewer's Question:

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

Sponsor's Response:

A response was received on June 23, 2107.

Reviewers Comment:

The sponsor's response was acceptable.

**CONCLUSION:**

Based on review of the data provided in the sections covered by this review the submission can be approved. The (b) (4) assay has not been properly validated, however, because of the low levels of (b) (4) present in the actual process samples, it is acceptable to perform appropriate validation of this assay as a post-marketing commitment.

*Bio Products Laboratory Inc. 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.*

*Final Report Submission: December 19, 2018*