



FOOD AND DRUG ADMINISTRATION

Center For Biologics Evaluation and Research

Memorandum

FROM: Tigist Kassa, Ph.D., LBVB/DBCD/OBRR/CBER; (240) 402-9622, FAX (301)595-1230

THROUGH: Abdu Alayash, Ph.D., Chief, LBVB/DBCD/OBRR/CBER; (240) 402-9350, FAX (301) 595-1230.

THROUGH: Oriji Illoh, M.D., Director, DBCD/OBRR/CBER; (240) 402-8457

TO: Wayne Hicks, Chair, LBVB/DBCD/OBRR/CBER; (240) 402-8197, FAX (301) 595-1126.

Lorraine Wood, Regulatory Project Manager

The file (BL 125644/0)

SUBJECT: Review of the Chemistry, Manufacturing, and Control sections of original Biologic License Application submission (BL 125644/0) for Bio Products Laboratory (BPL) Albumin (Human), 5%; Albumin (Human), 25%. Analytical Procedures and Method Validation sections: 3.2.S.4.2, 3.2.P.5.2, 3.2.S.4, 3.2.P.2, 3.2.P.3, 3.2.P.3.4, 3.2.P.3.5, are reviewed.

The submission BL 125644/0 was received 12-09-2016, and was given DCC login ID 650659

RECOMMENDED ACTION: Approval

The review of responses to the CR letter:

Questions on CR letter:

1. Regarding the validation of (b) (4) on linearity assessment, Table 29 (3.2.P.5.3 section 1.2.3.3 page 26), which was submitted on June 30, 2017 under Amendment STN 125644/0.22 in response to the information request question # 2, on May 5th, 2017
 - a. This response was submitted beyond June 21 and is considered to be open to further review.
 - b. You stated that the information given in 3.2.P.5.2 section 1.3.3 page 10 on (b) (4) representation ((b) (4)) assigned to (b) (4) respectively, is incorrect as it shows the calculation for Immunoglobulin products. Please provide an updated analytical procedure and validation report including the correct albumin calculation.

Sponsor Response:

a. In the previous response, BPL committed to update the Analytical Procedures section in the CTD (3.2.P.5.2 section 1.3.3 page 10) to correct the discrepancy. Section 12.2.1 and appendix VII of SOP QAC00457 (b) (4) has been updated with the statement below to clarify how the Albumin (b) (4) are reported. The data reported in the validation report LR/805/1/15/01 was based on the correct albumin calculation and therefore has not been changed.

Albumin samples – (b) (4)

Reviewer's comment: SOP is updated and response is acceptable.

2. Regarding the validation of (b) (4) for the determination of aluminium (3.2.P.5.3 section 1.2.5.2), which was submitted under Amendment STN 125644/0.22 in response to the information request question # 7, on May 5th 2017:

- a. This response was submitted beyond June 21 and is considered to be open to further review.
- b. You stated that (b) (4) Albumin ((b) (4)) was not used for the linearity test and that the range limit is incorrect for this assessment. It was also indicated in the submission that the intermediate precision assessment for batch (b) (4) did not meet the acceptance criteria. Please revalidate the method and provide the correct validation report.

Sponsor Response:

b. The first part of the question regarding the linearity was responded to as part of an Information Request (IR) dated 05th May 2017. The answer to this question was provided to the FDA on the 30th June 2017 under Question 7. BPL committed to correct the CTD section as the batch number (b) (4) was not used for the linearity test. The linearity test was performed using batch (b) (4).

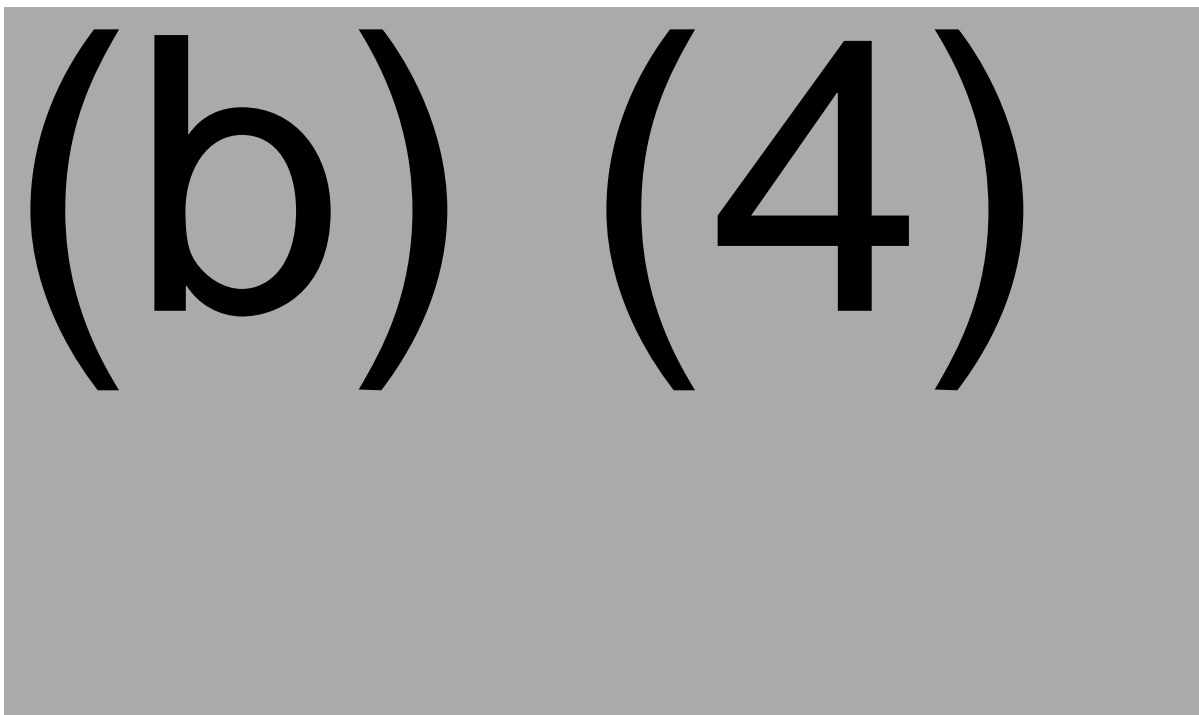
For the intermediate precision, the results obtained for the (b) (4) batches (b) (4) samples show quite a wide range of variability. The levels of aluminium in the samples were in most cases (b) (4) to the assay quantitation limit of (b) (4), which is around (b) (4) times (b) (4) the specification limit. This variability is not considered significant as the method is shown to be capable of detecting even the extremely low levels of aluminium seen in the samples. We did not revalidate as we consider that the accuracy data (% recovery) for the method has demonstrated that the assay is capable of accurately detecting quantifiable levels of aluminium from (b) (4), well below the specification limit, refer to LR/805/1/06/03, section 5.2. In addition, precision of the method has been demonstrated through the accuracy data, across (b) (4) batches, (b) (4) different operators on (b) (4) separate occasions, refer to table below.

The aluminium assay is used as a final product lot release test for Human Albumin Solution 5% and 25%. The Human Albumin Solution manufacturing process is very robust with regards to control of aluminium. (b) (4)

(b) (4) manufacturing process to Human Albumin Solution 5% and 25% to drug substance, shows that of (b) (4) final product batches, the mean aluminium content was (b) (4); and all were well below the final

product specification limit of not greater than 200µg/L. Aluminium levels are therefore demonstrated to be well controlled by the manufacturing process.

The validation report LR/805/1/06/02 has been replaced with LR/805/1/06/03 with an additional comment in section 6.2.



Reviewer's comment: *Response is acceptable.*

3. Regarding the validation of analytical procedures (b) (4) and the (b) (4) using (b) (4) – (Drug Substance, 3.2.S.4.3):

Please provide a detailed description of the conditions used for the assessments of repeatability and intermediate precision that includes variations in days, analysts, and equipment. The method validation should also include accuracy, linearity and specificity assessments.

Sponsor Response

The description of the conditions for the (b) (4) and (b) (4) method used for the assessment of repeatability and intermediate precision is provided in the procedure in sections 10 of SOP QAC/00313 (b) (4) and QAC/00457 (b) (4) respectively.

For the (b) (4) method: Section 10 of SOP QAC/00313 gives a detailed description of the testing procedure including preparation. Section 5 of the laboratory protocol LP/805/2/09/01 describes the sample type (in-process intermediates), storage condition (temperature (b) (4)) and the preparation method in section 9 of the same protocol.

The repeatability of the method was assessed by analysing (b) (4) replicates of the Albumin sample in one assay (b) (4) whilst the intermediate precision was assayed on (b) (4) different assays over (b) (4) period, by (b) (4) independent analysts using the same equipment (in section 9 of SOP QAC/00313).

For the (b) (4) method: Section 10 of SOP QAC/00457 gives a detailed description of the testing procedure including preparation. Section 5 of the laboratory protocol LP/805/2/15/01 describes the sample type (in-process intermediates), storage condition (temperature (b) (4)) and the preparation method in section 9 of the same protocol.

The repeatability of the method was assessed by analysing (b) (4) replicates of the Albumin sample in one assay (b) (4) whilst the intermediate precision was assayed on (b) (4) different assays over (b) (4) period, by (b) (4) independent analysts using the same equipment (in section 9 of SOP QAC/00457).

Both methods were previously validated using (b) (4) batches of Human Albumin Solution (5% and 25%) final product (validation reports LR/805/1/15/01 for (b) (4) and LR/805/1/09/01 for (b) (4)). The accuracy, linearity and specificity assessment for the methods were covered using final products and therefore were not included in this validation. The final product validation report is provided to assist this review.

SOP

- QAC/00313 (b) (4)

- QAC/00457 (b) (4)

Validation Protocols

- LP/805/2/09/01 (intermediates)

- LP/805/2/15/01(intermediates)

- LP/805/1/09/01(final product)

Validation Reports

- LR/805/2/15/01(intermediates)

- LR/805/2/09/01(intermediates)

- LR/805/1/15/01(final product)

Reviewer's comment: Response is acceptable.

4. Regarding the validation of analytical procedures for determination of (b) (4) (3.2.P.5.3), please submit an updated validation report that includes linearity assessment.

Sponsor Response:

(b) (4)

(b) (4)

Reviewer's comment: Response is acceptable.

SUBMISSION SUMMARY

Both Albumin 5% and 25% products are produced by Bio Products Laboratory Ltd (BPL) in Elstree, United Kingdom and are manufactured using (b) (4) plasma collected in FDA-inspected plasma collection centers located in the United States. It is a sterile liquid formulation for intravenous administration containing either 5% or 25% human albumin. The indications for both formulations are for the treatment of hypovolemia, burns, adult respiratory distress syndrome, cardiopulmonary bypass, liver cirrhosis and its complications, nephrotic syndrome, and ascites. It is supplied in a colorless, (b) (4) glass bottles providing 12.5 g and 25 g doses. The bottles are sealed using a halobutyl stopper, and an aluminum and polypropylene tamper evident cap. It has a shelf-life of 36 months when stored at below 30°C in its original packaging.

SECTIONS REVIEWED HEREIN:

Control of Drug Product (3.2.P.5)

- Specifications (3.2.P.5.1)
- Analytical Procedures (3.2.P.5.2)
- Validation of Analytical Procedures (3.2.P.5.3)
- Justification of Specification (3.2.P.5.6)

Control of Drug Substance (3.2.S.4)

- Specifications (3.2.S.4.1)
- Analytical Procedures (3.2.S.4.2)
- Validation of Analytical Procedures (3.2.S.4.3)
- Justification of Specification (3.2.S.4.5).

3.2.P.5.1 Specifications

Specifications for final product of Albumin (Human), 5% and 25% are provided and are summarized in the table below:

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 | | (b) (4) |
| Purity/Specific Function | Protein g/L, HAS 5% only | (b) (4) | (b) (4) | CFR 640.82 |
| | 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) | (b) (4) | CFR 640.81 |
| | Acetyltryptophanate, mmol/L | (b) (4) | (b) (4) | 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) |
| | (b) (4) | (b) (4) | | BPL |

Labelled Product Specification Tests

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

3.2.P.5.2 Analytical Procedures

Assays performed during lot release:

- 1) pH measurement ((b) (4))
- 2) Determination of thermal stability by incubating at 57 °C for 50h (21 CFR 640.82f).
- 3) Identification of Albumin using (b) (4)
- 4) Total protein measurement using (b) (4)
- 5) Determination of protein composition by (b) (4)
- 6) Measurement of (b) (4)
- 7) Measurement of sodium by (b) (4)
- 8) Measurement of Sodium Caprylate by (b) (4)
- 9) Measurement of Sodium Acetyltryptophanate by (b) (4)
- 10) Measurement of (b) (4)
- 11) Measurement of aluminium by (b) (4)
- 12) Measurement of potassium by (b) (4)
- 13) Measurement of (b) (4)
- 14) Measurement of (b) (4)

3.2.P.5.3 Validation of Analytical Procedures

1.2.1 Determination of pH

This method is performed per (b) (4) . In this assay the final product samples were (b) (4)

Parameters used for validation of the method:

Accuracy- (b) (4)

Precision (b) (4)

Intermediate Precision- (b) (4)

Linearity and Range are defined in the calibration process. Calibration acceptance limit is (b) (4), for a range of (b) (4) using standard calibration buffers.

Sensitivity- (b) (4)

Robustness- (b) (4)

Reviewer's comment: All measurements met the acceptance criterion; therefore, the method is validated.

1.2.3.2 Determination of total protein

Parameters used for validation of the method:

Specificity- (b) (4)

Accuracy- (b) (4)

Precision- (b) (4)

Linearity- (b) (4)

Range- (b) (4)

Robustness- (b) (4)

On April 7, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's Comment: Responses are acceptable and all measurements met the acceptance criteria; therefore, the method is validated.

1.2.3.2 Identification of Albumin using (b) (4)

BPL didn't describe which (b) (4) was used for the determination of the protein composition; additional information request was sent to the sponsor on May 5th, 2017; list of information requests and responses from the sponsor are compiled at the end of this memo.

The validation is performed for the following characteristics:

Specificity: (b) (4)

Accuracy: (b) (4)

Repeatability: (b) (4)

Intermediate Precision (b) (4)

Linearity: (b) (4)

Range: (b) (4)

Robustness (b) (4)

Reviewer's comment: Responses and validation studies are acceptable.

1.2.3.3 (b) (4)

(b) (4)

Validation is performed for the following parameters:

Specificity: (b) (4)
(b) (4)
(b) (4)

Accuracy: (b) (4)
(b) (4)
(b) (4)
(b) (4)

Repeatability: (b) (4)
(b) (4)
(b) (4)
(b) (4)

Intermediate precision: (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

Linearity: (b) (4)
(b) (4)
(b) (4)

Range: (b) (4)
(b) (4)
(b) (4)
(b) (4)

Robustness: (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

On May 5th, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's comment: The sponsor needs to update the analytical procedure and validation report.

Excipients

1.2.4.1 Determination of Sodium

(b) (4) was used for the determination of sodium. Concentration of sodium sample is determined by (b) (4)

The following validation parameters were performed:

Specificity: (b) (4)
(b) (4)
(b) (4)

Accuracy: (b) (4)
(b) (4)

Repeatability: (b) (4)
(b) (4)
(b) (4)

Intermediate Precision: (b) (4)
(b) (4)
(b) (4)

Linearity: (b) (4)
(b) (4)
(b) (4)
(b) (4)

Range: The range was determined from the linearity assessment.

On May 5th, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's comment: Responses and validations are acceptable.

1.2.4.2 Determination of Sodium Caprylate

(b) (4) was used to determine caprylic acid (octanoic acid) using (b) (4) as internal standard.

Specificity: (b) (4)
(b) (4)
(b) (4)

Accuracy: (b) (4)
(b) (4)
(b) (4)

Repeatability: (b) (4)
(b) (4)
(b) (4)

Intermediate Precision: (b) (4)
(b) (4)
(b) (4)

Linearity: (b) (4) [redacted]
[redacted]
[redacted]
[redacted]

Range: (b) (4) [redacted]
[redacted]
[redacted]

Robustness: (b) (4) [redacted]
[redacted]
[redacted]

On May 5th, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's comment: Responses and validation are acceptable.

1.2.4.3 Determination of Sodium Acetyltryptophanate

(b) (4) was used for the determination of sodium acetyltryptophanate.

Specificity: (b) (4) [redacted]
[redacted]
[redacted]
[redacted]

Accuracy: (b) (4) [redacted]
[redacted]
[redacted]

Repeatability: (b) (4) [redacted]
[redacted]
[redacted]

Intermediate precision: (b) (4) [redacted]
[redacted]
[redacted]

Linearity: (b) (4) [redacted]
[redacted]
[redacted]
[redacted]

Range: (b) (4) [redacted]
[redacted]
[redacted]

Robustness (b) (4)

The analytical procedure provided doesn't clearly describe what type of (b) (4) method is used for the determination of sodium acetyltryptophanate. On May 5th, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's comment: Responses and validation are acceptable.

1.2.5 Impurities

1.2.5.1 Determination of (b) (4) using (b) (4)

(b) (4) was determined by (b) (4) using (b) (4)

Specificity: (b) (4)

Accuracy: (b) (4)

Precision: (b) (4)

Linearity: (b) (4)

Range: (b) (4)

Robustness: (b) (4)

Reviewer's comment: All measurements met the acceptance criterion; therefore, the method is validated.

1.2.5.2 Determination of Aluminum by (b) (4)

Aluminum is determined by (b) (4). The concentration of aluminum in a sample is determined by (b) (4).

Specificity:

(b) (4)

Accuracy:

(b) (4)

Precision:

(b) (4)

Linearity:

(b) (4)

Range:

(b) (4)

Limit of Quantitation:

(b) (4)

Robustness:

(b) (4)

On May 5th, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's comment: Information provided for the linearity and range assessments are incorrect and the sponsor has agreed in their response dated (June 30th, 2017). In addition, it was indicated that the intermediate precision assessment for batch (b) (4) did not meet the acceptance criteria. Therefore, please revalidate the method and provide an updated validation report.

1.2.3 Determination of Potassium using (b) (4)

(b) (4) was used for the determination of potassium. Concentration of potassium sample is determined by (b) (4) t.

Specificity: (b) (4)

Accuracy: (b) (4)

Repeatability: (b) (4)

Intermediate Precision: (b) (4)

Linearity: (b) (4)

Range: (b) (4)

Limit of Quantitation: (b) (4)

Reviewer's comment: The validation is acceptable.

1.2.5.4 Determination of (b) (4)

(b) (4)

Validation: Only precision and robustness are reported.

Repeatability: (b) (4)

Intermediate Precision: (b) (4)

Robustness: (b) (4)

On May 5th, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's comment: Response and validation are acceptable.

1.2.5.5 Determination of (b) (4)

Principle: (b) (4)

(b) (4)

Specificity:

(b) (4)

(b) (4)

Accuracy:

(b) (4)

(b) (4)

Precision:

(b) (4)

(b) (4)

Quantitation Limit:

(b) (4)

(b) (4)

Linearity:

Linearity was not assessed.

Range:

(b) (4)

(b) (4)

Robustness:

(b) (4)

(b) (4)

On May 5th, 2017 CBER requested additional information from the sponsor; list of information requests and responses from the sponsor are compiled at the end of this memo.

Reviewer's comment: The sponsor should submit an updated validation report that includes linearity assessment.

3.2.P.5.6 Justification of Specification(s)

Outlines the rationale applied in setting the specifications for HAS 5% and 25% drug product.

The final product specifications for HAS 5 and 25 % meet the requirements in the (b) (4) [REDACTED], and 21 CFR 640.82.

3.2.S.4.1 Drug Substance Specification

(b) (4) [REDACTED]

[REDACTED]

(b) (4)

(b) (4) [REDACTED]

[REDACTED]

- [REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

Reviewer's comment: Please provide a detailed description of the conditions used for the assessments of repeatability and intermediate precision that includes variations in days, analysts, and equipment. The method validation should also include accuracy, linearity and specificity assessments.

On April 7th, 2017 CBER requested additional information from the sponsor. On May 11th, 2017 CBER received BPL's response. Questions and responses are listed below:

Reviewer's Question:

- 1) *Please provide current SOPs for all 3.2.P.5.2 Analytical Procedures.*

Sponsor's Response:

- 1) The current SOP's for all Analytical Procedures are attached (see Appendix 1 – 20).

Reviewer's comment: *The (b) (4) SOP you sent in response to our request for Albumin (b) (4) testing does not have information on the analysis of the (b) (4). Please provide details of the analysis and a representative image.*

Reviewer's Questions:

- 2) *Please respond to the following questions on 3.2.P.5.2 Analytical Procedure-1.3.1 Determination of Total Protein by (b) (4):*

a) The information provided does not clearly state what type of (b) (4) method is used. Please provide detailed information for this method as described in FDA's "Analytical Procedures and Methods Validation for Drugs and Biologics" Guidance for Industry. This guidance is available on the FDA website.

b) It is indicated that a reference standard is not used for the analytical procedure. Please provide justifications for not using reference standards to generate standard curves for determination of protein concentrations. We recommend the use of some other protein concentration determination methods to compare with the results determined by your (b) (4) method. Representative (b) (4) and standard curves should be submitted.

- 3) *Please respond to the following questions on 3.2.P.5.3 Validation of Analytical Procedures-1.2.3.1 Total Protein by (b) (4):*

a) Please clarify whether you have performed System Suitability of the method.

b) The information provided for Specificity assessment is not clear. Please provide detailed information along with representative (b) (4) for assessment of the method.

c) Please provide a detailed characterization of the secondary standard you used for the accuracy assessment.

d) Please explain why you have chosen (b) (4) as your target concentration throughout the analysis.

Sponsor's Response:

(b)
(4)

[Redacted text block]

[Redacted text block]

3. 3.2.P.5.3 Validation of Analytical Procedures-1.2.3.1 Total Protein by (b) (4) :

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

Reviewer's comment: Responses are acceptable.

On May 5th, 2017 CBER requested additional information from the sponsor. On June 30th, 2017 CBER received BPL's response. Questions and responses are listed below:

Reviewer Questions:

- 1) *The information provided for the (b) (4) does not clearly indicate the particular method used for the analysis. Please specify what type of (b) (4) method is used. Please provide representative images of the results.*

Sponsor's Responses

(b) (4)

[Redacted text block]

(b) (4)

Reviewer's comment: Responses are acceptable.

Reviewer Questions:

- 2) *Validation of (b) (4), 3.2.P.5.3 section 1.2.3.3:*

- a) *In the linearity assessment, Table 29 (3.2.P.5.3 section 1.2.3.3 page 26), please explain what (b) (4) represents. Analytical Procedures (3.2.P.5.2 section 1.3.3 page 10) states that (b) (4) represent (b) (4) respectively, however page 28 (3.2.P.5.3 section 1.2.3.3) indicates that (b) (4) represents the (b) (4). Please explain the discrepancy.*
- b) *Please clarify how many runs were done for robustness (Table 31, page 28, 3.2.P.5.3 section 1.2.3.3) testing for each modified condition.*
- c) *Please provide representative (b) (4) (raw data) for the (b) (4) analysis of the final products. In addition, please provide calibration curve for the standards that was used in the analysis.*

d) Please provide detailed information for System Suitability testing for the (b) (4) method.

Sponsor's Response

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

(b) (4)

[REDACTED]

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: *The sponsor needs to provide the updated analytical procedure and validation report with the correct albumin calculation.*

Reviewer Questions:

- 3) *Please explain the method you used for the determination of sodium. If it is an in house developed method, please provide detailed information for the method validation. Please specify the (b) (4) you used at the (b) (4) for the determination of sodium.*

Sponsor's Response

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: *Responses are acceptable.*

Reviewer Questions:

- 4) *For the determination of Sodium Caprylate using (b) (4), please confirm if you have performed system suitability. Please also provide representative (b) (4).*

Sponsor's Responses

- 4) BPL confirms that system suitability was performed as per section 10 of SOP QAC/00303 Octanoate (Sodium Caprylate) in Human Albumin Solution and all the acceptance criteria shown in appendix III of the SOP were met.

Representative (b) (4) are included in the Sodium Caprylate method summary provided.

| SOP | Method summary | Protocol | Report |
|-----------|-------------------------|----------------|----------------|
| QAC/00303 | Octanoate Determination | LP/805/1/07/01 | LR/805/1/07/01 |

Reviewer's comment: Responses are acceptable.

Reviewer Questions:

- 5) *For the method used for the determination of Sodium Acetyltryptophanate:*

- a) *Please clearly define what type of (b) (4) method is used. Furthermore, please clarify whether you have performed System Suitability for the method.*
- b) *Please provide representative (b) (4) (raw data) from the analysis.*
- c) *Please confirm that you have measured the (b) (4) for (b) (4) acetyl tryptophan to test the ability of the method to distinguish between the albumin (b) (4) and (b) (4) acetyl tryptophan.*
- d) *In the description of linearity assessment it is mentioned that a standard solution was used; however, the data in the table (table 46, page 39) shows results from different protein concentration of the 5% Albumin product. Please clarify the discrepancy. If standard solution is used, please give information about the source of the standard and the data found from the assessment.*

Sponsor's Response

For the determination of Sodium Acetyltryptophanate:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

(b) (4)

Reviewer's comment: Responses are acceptable.

Reviewer Questions:

6) For the determination of Aluminum using (b) (4) :

a) Please specify the (b) (4) at which the (b) (4) of aluminum is measured.

b) For the linearity assessment, the linearity assessment was done using batch (b) (4) (25% Albumin product) with the addition of aluminum standard solution of (b) (4). However, the data provided in the table (table 57, page 48) are from a different batch and product (b) (4), 5% Albumin product) with different amounts of aluminum standard solution added (b) (4). The plot of (b) (4) vs aluminum concentration for the data provided in the table loses linearity after the concentration of (b) (4) of Al, therefore the highest range limit should be this concentration of Al. Based on the observation on the data you provided in the table, (b) (4) are high concentrations and the correlation coefficient will not be in the limit. Please revise, or explain this assessment.

Sponsor's Response

(b) (4)

[REDACTED]

(b) (4)

[REDACTED]

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: *The sponsor needs to revalidate the method and provide correct validation report.*

Reviewer Questions:

- 7) *Please indicate the (b) (4) at which the (b) (4) were recorded in the analytical procedure and in the validation assessments. Please also provide the (b) (4) used for (b) (4) concentration calculation.*

Sponsor's Response

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: *Responses are acceptable.*

Reviewer's Questions:

8) Please clarify which standard is used for the determination of (b) (4) in routine testing, the (b) (4) (mentioned in the 3.2.P.5.2 Analytical procedures section 1.5.5) or In House Control (mentioned in method validation for (b) (4) determination). If it is In House Control, please provide the description that contains:

a. Preparation, storage, and stability of the standard

b. Calibration against (b) (4)

Sponsor's Response

(b) (4)

(b) (4)

Reviewer's comment: *Response is acceptable.*

CONCLUSION

Company responses after the CR letter have answered the requests mentioned in the CR letter and have updated the analytical procedures and validation reports. After reviewing the responses, there are no problematic issues identified from my review perspective that would preclude final approval of this product.