

July 14, 2017

Our Reference: BLA 125644

Bio Products Laboratory Inc.

ATTENTION: Mary Ann Lamb, PhD

302 East Pettigrew Street, Suite C-190
Durham, NC 27701

Dear Dr. Lamb:

Attached is a copy of the agenda for your June 14, 2017, Mid-Cycle Communication teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to Submission BLA BL125644 in your future submissions related to the subject product.

If you have any questions, please contact me at (240) 402-8439 or lorraine.wood@fda.hhs.gov.

Sincerely,

Lorraine Wood, MS, MLS (ASCP)^{CM}
Regulatory Project Manager
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application type and number: BLA 125644/o

Product name: Human Albumin Solution (HAS) 5% and 25%

Proposed Indication: Hypovolemia, Ascites, Burns, Nephrotic syndrome, Acute Respiratory Distress Syndrome (ARDS), Cardiopulmonary bypass, Liver cirrhosis

Applicant: Bio Products Laboratory

Meeting date & time: June 14, 2017, 11 a.m. to 12 p.m., EDT

Committee Chair: Wayne Hicks, PhD

RPM: Lorraine Wood, MS, MLS (ASCP)^{CM}

Attendees:

FDA Attendees

LCDR Kelly Abraham MPH, CPH, OBRR/RPMS
John Eltermann, RPh, MS, OCBQ/DMPQ
Wayne Hicks, PhD, OBRR/DBCD/LBVB
Yiping Jia, PhD, OBRR/DBCD/LBVB
Tigist Kassa, PhD, OBRR/DBCD/LBVB
Sonday Kelly, MS, RAC, PMP, OBRR/RPMS
Laurie Norwood, OCBQ/DMPQ
Priscilla Pastrana, PhD, OCBQ/DMPQ
Michael Strader, PhD, OBRR/DBCD
Lorraine Wood, MS, MLS (ASCP)^{CM}, OBRR/RPMS

Bio Products Laboratory (BPL) Attendees

Matt Bodiam – Technical Development Manager
Ade Fujamade – Regulatory Affairs Manager
Helena Kelly – Head of QC
Sarah Kingsland - Bioanalytical Manager
Richard Kwofie – Method Development Specialist
Mary Ann Lamb – US Agent for BPL, Ltd
John More – Head of Research & Development
Ioannis Tsakas-Ampatzis - Programme Manager
Shirley Waterhouse – Stability

Agenda:

The Mid- Cycle Telecon Agenda was submitted to BPL on June 12, 2017.

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the review committee to date.

FDA stated that it would not discuss each outstanding information request items listed in the mid-cycle telecon agenda submitted to Bio Products Laboratory (BPL) on June 12, 2017. FDA stated that BPL will need to give timelines of anticipated response to the outstanding items.

BPL stated that they will supply an updated list of the outstanding information request with the response timeframes by Wednesday, June 21, 2017.

FDA stated that the review issues may change as the review progresses.

BPL stated that they wanted to briefly go over the first nine items listed in the mid-cycle telecon agenda.

Discussion Item Number One: Viral Validation/Viral Reduction

BPL stated that this information request was received on May 12, 2017, and they submitted their response to this request on June 2, 2017. BPL stated that Albumin is a product that has been on the market for 30 years. BPL provided HIV inactivation data and the range of enveloped and nonenveloped viruses. BPL provided a range, most of which are more resistant than HIV, which is why BPL did not perform the HIV study. BPL stated that they understand that a HIV study needs to be performed on the process itself. BPL suggested this study as a Postmarketing Commitment (PMC).

FDA stated that this is still being discussed internally with OBRR leadership. In addition, FDA stated they will send BPL a response in writing on this issue about the HIV study before the Late Cycle Meeting (LCM) tentatively scheduled for August 24, 2017.

FDA post meeting note:

Although there was discussion on BPL committing to perform a HIV study as a PMC, PMC negotiations will occur on or after November 9, 2017.

Discussion Item Number Two: Method Validation

BPL questioned the FDA regarding its concern about an additional method of validation.

FDA stated that the interpretation about (b) (4) testing and other issues raises concern. The methods performed have not been properly validated and some of

the tests failed validation. BPL will need to provide the raw data. BPL provided summary data that does not allow for a proper review of the data.

BPL stated that they will provide validation reports for each method.

FDA stated that all of the tests that were performed should have raw data submitted to the FDA. These issues were documented in the information request.

BPL questioned if the FDA will like to see individual data points instead of the aggregate or the summary.

FDA stated that they will like to review the individual data points and statistical treatment in order to analyze how the data was processed.

Discussion Item Number Three: Raw Data and Figures

BPL stated that they have not responded to the original question that was submitted as an information request. BPL stated that they will generate a table with drug substance characterization, methods and protocols. BPL asked the FDA what additional descriptive text will be helpful to facilitate the review.

FDA stated that the descriptive text should state what method was used, how the method functions, basic principle, background information on the material and equipment used, raw data and how errors were calculated. There needs to be a complete understanding of the process and how the samples were treated. BPL can provide the Standard Operating Procedure (SOP) in addition to the information requested.

BPL stated that they will submit the information by the end of June 2017.

Discussion Item Number Four: Impurities

BPL stated that they will provide the data for the drug substance and table of contents section and the SOPs as soon as possible.

Discussion Item Number Five: Drug Substance Specifications

BPL stated that this response is currently outstanding. Information on the drug substance is located in section 3.2.S.4.5, which is the (b) (4) [REDACTED]. Impurity specifications are set the same as the final product, (b) (4) [REDACTED]. BPL indicated they will submit SOPs, validation protocols, and reports for both the (b) (4) [REDACTED] specifications.

FDA stated that the raw data is needed to understand the process by which the data was generated.

Discussion Item Number Six: Stability

BPL stated that they have (b) (4) [REDACTED] pilot scale batches for 18 months, (b) (4) [REDACTED] manufacturing batches at pilot for 6 months, 9 months, and (b) (4) [REDACTED] to 6 months. BPL stated

that they will submit the current data by the end of June 2017. Twelve month data for PPQ batches is ongoing and BPL agreed to supply data before the Late Cycle Meeting tentatively scheduled for August 24, 2017.

FDA agreed with this proposal.

Discussion Item Number Seven: In –House Standards

BPL stated that they will provide the SOPs to respond to this question about internal flow charts and stability of their standards.

Discussion Item Number Eight: System Suitability

BPL stated that they submitted their response to the FDA on May 11, 2017. The testing was performed. The system suitability testing will be provided to FDA.

FDA agreed with this proposal.

Discussion Item Number Nine: Analytical Procedures

BPL stated that they have provided SOPs for drug substance and drug substance methods.

FDA stated that in reviewing this submission there were numerous examples of lack of details and information. For guidance BPL should refer to the FDA Guidance for Industry Drug Product Chemistry Manufacturing and Controls. The lack of details and information came up across a number of tests and review disciplines. Great attention to details is needed to demonstrate the reliability and quality of BPL testing to FDA.

BPL summarized the FDA wants to review the SOPs in addition to the summary of procedure and overview of what was used to qualify that procedure.

FDA stated that yes; this is an integral part of the Chemistry Manufacturing and Control (CMC) section of the BLA. All tests should be described in the methods and how the testing was performed.

2. Information regarding major safety concerns.

FDA stated that there are some safety concerns with the viral validation studies as mentioned in Discussion Item Number One.

BPL questioned if there were any clinical information questions.

FDA stated that there was not any concerns related to clinical at this time. However, the FDA indicated the description of vessels was in question. FDA stated that BPL will need to provide a copy of the diagram, and major and minor components, in addition to the contents of the components and sterilization. FDA questioned BPL on how they removed prions from the plasma.

BPL stated that they only use United States (b) (4) plasma, so the risk of BSE/TSE associated with plasma sourced from the United Kingdom is not an issue.

3. Preliminary review committee thinking regarding risk management.

The current thinking of the review committee is that a Risk Evaluation and Mitigation Strategy (REMS) is not required.

4. Any information requests sent and responses not received.

BPL stated that they would submit a timeline of when they will submit responses to the outstanding information request by June 21, 2017.

FDA pointed out that response to information requests had been very slow and this was impacting the reviewers' ability to effectively review the information within the constraints of the review clock. For example, FDA pointed to the IR requested on March 3, 2017, for which a response has not been received.

BPL stated that they felt they had addressed some of the requests indirectly. FDA then stated that each information request item required a complete direct response. FDA clarified that indirect responses are not sufficient.

5. Any new information requests to be communicated.

This was provided in the Mid-Cycle Telecon agenda submitted to BPL on June 12, 2017.

6. Proposed date(s) for the Late-Cycle meeting (LCM)

- a.** The LCM between you and the review committee is tentatively scheduled for August 24, 2017.
- b.** We intend to send the LCM meeting materials to you approximately 12 days in advance of the LCM.
- c.** If these timelines change, we will communicate updates to you during the course of the review.

7. Updates regarding plans for the AC meeting.

This application will not be presented to an Advisory Committee.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

No additional milestone dates to be discussed at this time.

Additional Discussion

The Division of Manufacturing and Product Quality (DMPQ) stated that a list of potential review issues were submitted to BPL in the filing with deficiencies letter dated February 7, 2017. Consequentially FDA and BPL held a telecon on March 13, 2017, to discuss the deficiencies listed in the filing letter. BPL agreed to submit the information to these deficiencies on March 31, 2017, and April 21, 2017. BPL submitted seven amendments to this application in response to these deficiencies. The information associated to these amendments was reviewed. The following deficiencies were identified after the review of the original application and the seven amendments:

Equipment:

1. Incomplete description of dedicated and shared equipment to be used for the manufacture of HAS 5% and 25%;
2. Deficient equipment Performance Qualification (PQ) studies. Specially, PQ studies that the firm considered acceptable, no matter that PQ testing has failed the acceptance criteria established in the PQ protocol.
3. Missing equipment performance qualification studies;
4. Missing information for the lifetime validation studies of the (b) (4) to determine the number of times that they can be used during routine production.

Container/Closure System:

5. Missing summary report for the Container Closure Integrity Testing (CCIT) for HAS 5% and 25% Drug Product;
6. Missing explanation for the use of (b) (4) types of stoppers and overseal caps in the reports for the PPQ studies in support for this application.

Contamination and Cross-contamination Controls:

7. Missing description of the containment, segregation, cleaning, sterilization, (b) (4), removal of prions, change over and line clearance controls; in addition, contamination, cross-contamination and mix-up prevention controls for dedicated and shared equipment to be used for the manufacture of Albumin products;
8. Missing summary reports of sterilization and (b) (4) validation studies for dedicated and shared equipment to be used for the manufacture of Albumin products;

9. Missing description of cleaning and removal of prions procedures for (b) (4) ;
10. Missing summary reports of cleaning validation studies for (b) (4) .

Water System:

11. Missing Water System Monitoring Program description, including testing conducted, acceptance criteria, and results from 2016.

Batch Records and Process Performance Qualification (PPQ) Study Reports:

12. Missing information in batch records and PPQ study reports. Specially, bioburden, sterility and environmental monitoring results were not included in the batch records and PPQ reports;
13. Incomplete description of the deviations initiated in the PPQ studies, included the actions taken to resolve and close these deviations.
14. Missing batch records.

END