FOOD AND DRUG ADMINISTRATION

Center For Biologics Evaluation and Research

Memorandum

DATE: May 6, 2011

FROM: Yiping Jia, Ph.D., LBVB/DH/CBER, HFM-343

THROUGH: Abdu Alayash, Ph.D., Chief, LBVB/DH/CBER, HFM-343

TO: Crystal Allard, CSO/Regulatory Project Manager, DBA/CBER, HFM-380
The file (STN125384)

SUBJECT: Review of the Chemistry, Manufacturing, and Control sections of original Biologic License Application submission (STN125384/0) by Kedrion, S.p.A., of a 25% Human Albumin Solution, i.e. KEDBUMIN.

The submission STN125384/0 is dated 07-30-2010, and was received 08-03-2010. This BLA could be found in its entirety in the EDR. Paper copies were not distributed as there were very few. The recommendations, overview of these submissions, the summary and comments are as follows:

Recommendation: Approval

All questions and request for information related to the review of this BLA, have been responded to and provided by the sponsor, and found to be acceptable. These include questions related to the CMC section of the BLA, which have been addressed and resolved during the course of this review cycle, through a number of information request (IR) and telecons, and the pre-licensing inspection. These review and inspection activities have led to the resolution of the outstanding issues, and completion of the BLA review, thereby permitting licensure of Kedrion's 25% Albumin (Human) without the issuance of a complete response letter.

Overview:

On behalf of Kedrion, S.p.A., Loc. Ai Conti, 55051 Castelvecchio Pascoli, Barga (Lucca) Italy, FFF Enterprises, Inc., 41093 County Center Drive Temecula, CA92591 submitted this original Biological License Application (BLA) for KEDBUMIN. KEDBUMIN is a 25% Human Albumin solution derived from U.S. plasma donors and produced by Kedrion, S.p.A. from an albumin paste intermediate ----------(b)(4)----------. The letter of authorization was included for ----------(b)(4)----------.

Kedrion, S.p.A. proposed the following indications for the use of KEDBUMIN:

- Hypovolemia: Restoration and maintenance of circulating blood volume where volume deficiency is demonstrated and colloid use is appropriate.
- Hypoalbuminemia: When the albumin deficit is the result of excessive protein loss, the effect of albumin administration will be temporary unless the underlying disorder is reversed.
- Prevention of central volume depletion after paracentesis due to cirrhotic ascites.
- Ovarian hyperstimulation syndrome (OHSS).
- Adult Respiratory Distress Syndrome (ARDS).
- Burns
- Hemodialysis: For patients undergoing long term dialysis or for those patients who are fluid-overloaded and cannot tolerate substantial volumes of salt solution for therapy of shock or hypotension.
- Cardiopulmonary Bypass Procedures: As part of the priming fluid.

KEDBUMIN is currently manufactured by Kedrion S.p.A., Loc. Ai Conti, 55051 Castelvecchio Pascoli, Barga (LU), Italy, at its manufacturing facility in Bolognana, Gallicano, Lucca. KEDBUMIN contains 250 g/L of plasma protein of which human albumin constitutes at least 96%. UMAN ALBUMIN has been marketed in Italy for over 40 years. In order to produce a product suitable for the US market, an albumin paste intermediate ----------(b)(4)----------. The raw material is obtained from Source Plasma that is collected in licensed US plasmapheresis centers according to FDA and EU regulations.

Reviewer responsibilities for this original BLA were as follows:

Chair/CMC product review: Yiping Jia

Administrative/Regulatory Project Manager: Crystal Allard

Pre-Clinical Toxicology/Pharmacology: Paul Buehler

Clinical Pharmacology and Clinical Data: Larry Landow

Statistical Analysis: Shiowjen Lee

Epidemiology: Craig Zinderman

Proprietary Name and Labeling: Alpita Popat (former reviewers: Michael Brony, Jean Makie)

Assays validation: Wayne Hicks

Establishment: Sean Byrd, Lori Peters

Pre-licensing Inspection: Lori Peters, Sean Byrd, Yiping Jia

Bioresearch Monitoring Inspections: Lillian Ortega

This memo concerns review of the Chemistry, Manufacturing, and Controls portion of the BLA and follows the outline in the *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma, or Serum-Derived Products (1999).* Various memos for the review of certain sections of the CMC portion of the BLA, and for Pre-Clinical Toxicology/Pharmacology, Clinical Pharmacology, Clinical Data, Statistical Analysis of Clinical Data, Labeling and Proprietary Name, Establishment, and Bioresearch Monitoring (BiMo), as well as the results of the pre-licensing inspection are to be submitted to STN 125384/0 separately.

The reviewer's summary and comments:

Drug Substance:

USP name: Albumin (Human)

Nonproprietary name (USA): Albumin (Human) 25%, USP

Name of drug substance: Human Albumin Solution

Name of drug product: KEDBUMIN

Manufacturer: (b)(4) production sites are involved.

----------(b)(4)----------.
Kedrion S.p.A.: from precipitated albumin paste to bulk Albumin (Human) 25%

Manufacture of Bulk Albumin (Human) 25% at Kedrion S.p.A.:

Shipping Albumin Paste to Kedrion S.p.A.

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----------(b)(4)----------

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---------(b)(4)----------:

---(b)(4)----------.

2 pages redacted (b)(4)

----------(b)(4)----------

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Stability batches:

For stability testing, (b)(4) batches of albumin paste were further processed by Kedrion to obtain three stability lots of finished Albumin (Human) 25% (----------(b)(4)----------). Kedrion's proposal for the stability study plan and its suitability for supporting the BLA for KEDBUMIN were acceptable by FDA (Notification letter – Reference CRMTS # 6974 Ref# PS000498 dated June 15th, 2009 and subsequent response from FDA dated July 7th, 2009).

For the first batch (b)(4), submitted previously in the Pre-IND package data on 24 February 2009, the in-process controls and finished product specifications follow the EU specifications as authorized for the product UMAN ALBUMIN, marketed by Kedrion in Italy and several other countries for over 40 years for the 20% formulation (the 25% formulation is on the Market since 1984 with an international approval date of May 5th, 1984). For the other two batches (-------(b)(4)---------) the in-process controls and finished product specifications follow FDA requirements. All the results are within the defined specifications for the three stability batches.

Conformance Batches:

Three conformance lots (----------(b)(4)----------) were prepared at Kedrion with albumin paste manufactured in accordance with 21 *CFR 640.81* - 84. In-process testing during the production of the three conformance lots of Albumin (Human) 25% manufactured with -(b)(4)- Albumin Paste were summarized, and the results were all within the required acceptance criteria.

NOTE that CBER policy requires that a firm seeking exemption from lot-by-lot release must submit information and data as directed in the "Guidance on Alternatives to Lot Release for Licensed Biological Products" (Federal Register Vol. 58, No. 137, July 20, 1993, pp.38771-3), which describes the prior history and test that are required to such requests.

IR letter question: Please follow FDA procedures for conformance lot samples and release protocol submissions which are part of the requirements for a BLA approval.

The sponsor's response: Conformance batches were shipped to CBER on February 7th, 2011 following the request from Crystal Allard dated January 21st, 2011. Kedrion will comply with any additional information requests concerning the conformance batches submitted for testing.

Reviewer's comment: the response is acceptable.

Process validation:

1. Transport of Albumin Paste from the --(b)(4)-- plant to the Kedrion plant
2. Development of the Albumin (human) 25% Production Process at Kedrion S.p.A.

A comparison of the Kedrion and --(b)(4)-- processes to prepare the Fraction V intermediate was submitted to FDA on 24 February 2009 in a Pre-IND dossier and discussed during a Pre-IND meeting with CBER on 26 March 2009.

The bulk product is virus inactivated by ethanol precipitation steps (----------(b)(4)----------). Albumin (Human) 25% solution (for intravenous use) is manufactured at Kedrion at an industrial production scale that includes heat treatment step (60°C ± 0.5°C for 10 - 11 hours) of the final product for viral inactivation in compliance with the requirements of the 21 *CFR 640.81* - 84. Effectiveness of the viral inactivation steps throughout the manufacturing processes performed at ----------(b)(4)---------- Kedrion is documented in viral validation studies.

Product characterization:

Human albumin solution is a natural product derived from plasma. The impurities possibly present in the final product may be product related, process related and/or contaminants, as discussed below by the sponsor.

Product related impurities: ----------(b)(4)---------- can be considered impurities in the final formulation of human albumin; according to Kedrion specifications, in compliance with -(b)(4)-, they should not be ----(b)(4)----. The manufacturing process followed by Kedrion provides a human albumin solution, both structurally and functionally intact, essentially constituted by molecules in monomeric form.

Process related impurities: -(b)(4)- and aluminum are removed to defined limits of --(b)(4)-- and ≤ 200 μg/L respectively.

Host related: Adventitious viral and bacterial contaminants might be present in the final product. Viral safety is assured by control of the starting material, human Source Plasma that is performed according to FDA and EU regulations and by viral validation studies.

Reviewer's comment: For product characterization, please provide additional information to the impurity profiles, including the summary of test results of accompanying plasma proteins such as ----------(b)(4)----------.

The sponsor's response: Kedrion provided a characterization study to assess any impurities which may be present. This includes the following plasma proteins: ----------(b)(4)---------- is not included in the study because it is a release specification carried out on each lot of finished product (acceptance criteria -(b)(4)-). (b)(4) is also a stability parameter.

As shown by the results obtained on the three conformance batches of KEDBUMIN, namely ----------(b)(4)----------, the (b)(4) content is always under the quantitation limit of ----(b)(4)--.

Reviewer's comment: the response is acceptable.

----------(b)(4)----------:

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Drug Product:

KEDBUMIN, Albumin (Human) 25%, is filled into (b)(4) glass bottles (filling size 50 mL).

Active Pharmaceutical Ingredient (API): Human plasma proteins containing at least 96% albumin

Excipient: sodium caprylate (octanoate), 20 mmol/L
N-acetyl-DL-tryptophan, 20 mmol/L

Other ingredients: Water for injection
Total Na^+ concentration

Formulation development: The drug product KEDBUMIN (25%) is manufactured using a consolidated industrial process and no special formulation has been developed by Kedrion S.p.A.

Batch formulation:

The quantity of Albumin (Human) 25% bulk solution used in production ranges from ---------(b)(4)---.

Standard production of KEDBUMIN (25%) with a nominal volume of 50 mL: ----------(b)(4)----------.

A flow diagram is provided as follows:

----------(b)(4)----------

↓
-------(b)(4)----------
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----------(b)(4)------------
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----(b)(4)-----
↓
Heat treatment
↓
Incubation ---(b)(4)---
(Sample: drug product)
↓
Visual inspection
↓
Labeling
↓
Packaging
↓
DRUG PRODUCT *KEDBUMIN, 25%*
↓
General warehouse Storage ≤ 30°C

----------(b)(4)---------- viral inactivation of filled product by heat treatment.

Sodium caprylate and N-Acetyl Tryptophan are the excipients present in the final product formulation. The quality of the excipients is guaranteed by the certificates of analysis provided by the supplier and by the controls performed at Kedrion following the relative monographs of the ----------(b)(4)----------. Kedrion also carries out the test for bacterial endotoxins, using the same (b)(4) method as for the finished product.

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----------(b)(4)----------:

a) ----------(b)(4)----------

b) ---------(b)(4)----------

c) ---------(b)(4)----------

d) ----------(b)(4)----------

----------(b)(4)----------:

----------(b)(4)----------:

a) ----------(b)(4)----------

b) ----------(b)(4)----------

c) ----------(b)(4)----------

d) ----------(b)(4)----------

e) ----------(b)(4)----------

The manufacturing process of the human albumin solution 25%, manufactured in accordance to *21 CFR 640.81-84,* was validated by execution of three batches.

Controls of Drug Product (KEDBUMIN, solution for infusion)

KEDBUMIN is a clear slightly viscous liquid, almost colorless, yellow, amber or green, obtained from human plasma which complies with specifications as follows:

Tests	**Specifications/limits**
Character	A slightly viscous liquid, it is almost colorless, yellow, amber or green
Total protein (g/L)	235 - 265
pH	6.4 - 7.4
----------(b)(4)---------	--------(b)(4)-------
Identity	The main component of the preparation corresponds to main component of human serum
Protein composition (%)	≥ 96
Sodium (mEq/L or mmol/L)	130 - 160
Potassium (mEq/L or mmol/L)	≤ 2
Aluminum (ppb or µg/L)	≤ 200
-------(b)(4)------	(b)(4)
----------(b)(4)----------	-(b)(4)-
----------(b)(4)---------	----------(b)(4)-----------
Sterility	Sterile
Pyrogens	Pyrogens free (-----(b)(4)--------)
Sodium caprylate (mmol/g proteins)	0.064 – 0.096
N-Acetyl-DL-tryptophan (mmol/g protein)	0.064 – 0.096
-------(b)(4)------	(b)(4)
Heat Stability (50 hrs/57°C)	Unchanged after 50 h at 57°C
General safety	-------(b)(4)---------- No unexpected response or weight loss in mice and guinea pigs after 7 days
-------(b)(4)------	(b)(4)
----------(b)(4)------------	---(b)(4)---
-------(b)(4)------	(b)(4)

*Results are not reported on the certificate of analysis.

Analysis of results from three batches manufactured for stability purpose (Batches No.-------(b)(4)----------) and three conformance batches (Batches No.----------(b)(4)----------) (KEDBUMIN (25%) 50 mL) are provided.

The specifications reported for batch No. -(b)(4)-, submitted with the pre-IND dossier on 24th February 2009, are in compliance with EU specifications. Differences with respect to US requirements are protein composition, pH, total protein, Na+ concentration, --------(b)(4)-------- limits. For the stabilizers Sodium Caprylate and N-Acetyl Tryptophan a different but equivalent way of expressing the units is used. Furthermore, general safety testing required by *21 CFR 600* has not been carried out.

Results obtained for the stability batch No. -(b)(4)- are within the acceptance limits and in compliance both to EU and US requirements. With regards to the other two stability batches and the three conformance batches, results are within the acceptance criteria.

Reviewer's comment: please advise the firm that the performance of the General Safety Test on final container product lots is mandatory, and that a lot-by-lot release could not be waived until a sufficient history of quality and compliance is accrued by the firm.

The sponsor's response: Kedrion confirms that the General Safety test will be a release specification for all the batches that will be marketed in US.

Reviewer's comment: the response is acceptable.

Stability [KEDBUMIN (25%), solution for infusion]

Stability of the finished product:

A stability study was initiated to verify the albumin solution maintains its physico-chemical and biological characteristics for a period of 3 years when stored at a temperature of 30 (b)(4)°C.

Real time and accelerated studies were carried out under the following conditions:

Study	**Temperature**	**MONTHS**					
Real time	30°C (b)(4)	0	6	12	24	36	(b)(4)
Accelerated study	---(b)(4)---	--	--	--	--	--	

Reviewer's comment: Please verify that in addition to the proposed time points of the long term stability study at 0, 6, 12, 24, 36, (b)(4) months, more time points are needed at 3, 9, and 18 months. Please also note that updated stability data from the conformance lots should be submitted for review prior to the final approval of the product.

The sponsor's response: An update of the stability data of the three conformance batches (----------(b)(4)----------) is provided. The accelerated stability study is concluded; long-term stability results at 6 months show that all the specifications are met. At present the stability program is at 10 months; Kedrion commits to provide a further update at 12 months. Kedrion agrees to add the check point at 18 months for the second year of stability. The stability protocol will be amended accordingly.

Reviewer's comment: This issue was further discussed during inspection and the stability program was amended accordingly.

Biochemical controls:

• ----------(b)(4)----------

• Protein composition (Albumin ≥ 96%)

• Total protein (235 – 265 g/l)

• pH (6.4 – 7.4)

Chemical controls:

• Character (A clear slightly viscous liquid, it almost colorless, yellow, amber or green)

• Aluminum (≤ 200 µg/L)

• ----------(b)(4)----------

Microbiological control:

• Sterility* (sterile)

• *This test is performed only at the time of release (and will be tested at the end of shelf life).*

For accelerated stability testing at ----(b)(4)---, results at this storage temperature for all tested parameters were found within the limits. The study was completed for all three batches manufactured for the purpose of establishing stability of the product.

For long term stability testing at 30°C (b)(4), available long term stability data showed all parameters tested up to date were within both the US and EU requirements. The studies are on-going.

The stability study report (STB-002-D) related to the EU product UMAN ALBUMIN 25% has been already submitted with pre-IND package data on 24th February 2009. This study confirms a shelf life of 3 years. Although the stability specifications, namely protein composition, total protein, pH, and (b)(4) are in compliance with the EU requirements, the results are also all within the US requirements and remain unchanged over the 3 years stability period. On the basis of the stability data so far obtained and the data available for the EU product UMAN ALBUMIN, no significant difference is expected in the results of the stability studies which are still ongoing. A shelf life of 36 months is proposed for the product KEDBUMIN. After licensure of the product, one batch of KEDBUMIN (25%) per year will be placed into the stability program.

Reviewer's comment: Protein composition of Albumin (Human) products appeared as (b)(4) in this BLA submission, rather than no less than 96% as committed previously. Please confirm all your commitments made during your meetings with the FDA regarding Kedbumin occurred prior to the BLA submission.

The sponsor's response: Kedrion confirms that acceptance criteria for protein composition for batches intended for US market is no less than 96% according to the CFR *Title 21, subpart H Albumin (Human) Sec 640.82,* as reported in the CMC section provided to FDA in the BLA application dossier. Kedrion would like to clarify that only the specifications reported for batch ----(b)(4)----, submitted with the pre-IND dossier on 24th February 2009, are in compliance with

EU specifications. This lot refers to an albumin batch manufactured only for stability purpose. Differences with respect to US requirements are protein composition, pH, total protein, Na+ concentration, -----(b)(4)---, and (b)(4) limits. For the stabilizers Sodium Caprylate and N-Acetyl Tryptophan, a different but equivalent way of expressing the units is used. Furthermore, general safety testing required by *21 CFR 600* has not been carried out. However the results obtained for the stability batch No -(b)(4)-- are within the acceptance limits and in compliance both to EU and US requirements.

Reviewer's comment: the response is acceptable. Kedrion also submitted on 4/29/2011 the updated stability data at 12 months for the three conformance batches ----------(b)(4)----------, as well as data at 36 months for the stability batch ---(b)(4)--. All results met specifications.

Adventitious Agents Safety Evaluation (KEDBUMIN, Kedrion S.p.A.)

KEDBUMIN (25%) is manufactured by Kedrion S.p.A. starting from an intermediate albumin paste ----------(b)(4)----------. For the product KEDBUMIN (25%), manufactured starting from the ---(b)(4)--- intermediate, the following manufacturing steps were validated for their ability either to remove or inactivate potential viral and non-viral adventitious agents:

----------(b)(4)----------
----------(b)(4)----------
3rd step) Fractionation of Effluent I to Effluent II+III – ----------(b)(4)----------
4th step) Fractionation of Effluent IV-1 to Effluent IV-4 – ----------(b)(4)----------
5th step) Depth filtration of Fraction V suspension – ----------(b)(4)----------
6th step) Heat treatment – Kedrion

The overall safety of KEDBUMIN (25%) was evaluated by combining the viral inactivation/removal capacity of the manufacturing steps carried out ----------(b)(4)---------- by Kedrion (step 6) and by summing-up logarithmic reduction factors from each significant step (with reduction factors ≥ 1).

----------(b)(4)----------

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----------(b)(4)----------
----------(b)(4)----------
----------(b)(4)----------
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----------(b)(4)----------

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----------(b)(4)----------.

The viral validation studies carried out ---(b)(4)--- were provided in the ----------(b)(4)----------, and the letter of authorization was provided to this BLA. One step of the manufacturing process was carried out by Kedrion and was validated for its ability to inactivate viruses:

6th step) Heat treatment (HIV, BVDV, Reo, PsRV) – Kedrion

• Human Immunodeficiency Virus type I (HIV), an enveloped human retrovirus. This virus also serves as a model for Human Immunodeficiency Virus type 2. It is effectively removed by inactivation methods, ----------(b)(4)----------.

• Bovine Viral Diarrhoea Virus (BVDV), an enveloped RNA virus. It is an accepted model for Hepatitis C Virus as currently no methods are available for the propagation of HCV. Inactivation methods, ----------(b)(4)----------.

• Pseudorabies Virus (PsRV), an enveloped DNA virus. It is a model virus for human Herpes Viruses and Hepadnaviridae; currently, there is not practical test system for Hepatitis B virus validation. It is effectively affected by inactivation methods, ----------(b)(4)----------.

• Reovirus type 3 (REO), a non-enveloped RNA viruses. It is a model virus for Hepatits A virus (HAV). It is susceptible to inactivation methods, ----------(b)(4)----------.

The reduction factors as well as the initial and final viral charges for the heat treatment step under standard conditions and under worst conditions for Albumin 25% are as follows:

[(b)(4)]

[(b)(4)]

By combining the viral inactivation/removal capacity of the manufacturing steps carried out ----------(b)(4)---------- and by Kedrion (step 6) and by summing-up logarithmic reduction factors from each significant step (with reduction factors ≥ 1), the overall reduction factors for the manufacturing of KEDBUMIN 25% were obtained.

Adventitious Agents Safety Evaluation

Step	**Test Virus**	**Mean Reduction Factor (log10) Albumin 25%**
Fractionation of Effluent I to Effluent II +III [a]	HIV-1	3.4
Depth Filtration of Fraction V suspension	HIV-1	3.4
Heat treatment	HIV-1	(b)(4)
Overall Reduction Factor		**(b)(4)**
Fractionation of Effluent I to Effluent II +III [a]	BVDV	3.5
Heat treatment	BVDV	> 5.17
Overall Reduction Factor		**> 8.67**
Fractionation of Effluent I to Effluent II +III [a]	PRV	3.9
Depth Filtration of Fraction V suspension	PRV	≥ 3.4

Heat treatment	PRV	> 5.07
Overall Reduction Factor		**≥ 12.37**
Fractionation of Effluent I to Effluent II +III a	REO	2.1
Fractionation of Effluent IV-1 to Effluent IV-4 [a]	REO	(b)(4)
Depth Filtration of Fraction V suspension	REO	4.9
Heat treatment	REO	4.62
Overall Reduction Factor		**(b)(4)**
Fractionation of Effluent I to Effluent II +III a	PPV	1.0
Fractionation of Effluent IV-1 to Effluent IV-4 a	PPV	(b)(4)
Depth Filtration of Fraction V suspension	PPV	4.2
Overall Reduction Factor		**(b)(4)**
Fractionation of Effluent I to Effluent II +III a	HAV	1.4
Fractionation of Effluent IV-1 to Effluent IV-4 a	HAV	(b)(4)
Depth Filtration of Fraction V suspension	HAV	2.0
Overall Reduction Factor		**(b)(4)**
Fractionation of Effluent IV-1 to Effluent IV-4 a	EMCV	3.7
Overall Reduction Factor		**3.7**

For all enveloped viruses, HIV-1, BVDV, PRV, and the non-enveloped Reo virus, an overall reduction factor greater than 8 logs was obtained. For PPV an overall reduction factors greater than (b)(4) were obtained.

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----------(b)(4)----------.

Heat pasteurization

The aim of the validation study was to determine the efficacy and reproducibility of heat treatment according to the parameters prescribed by the (b)(4) (T 60 ± 0.5°C for 10 - 11 hrs). Minimum and maximum loads were considered. During the validation study maximum temperature, minimum temperature, average temperature, and difference between maximum and minimum temperature were evaluated.

Reviewer's comment: In Figure A.2-1, Module 3.2.A.2, the heat treatment step is ----------(b)(4)----------. Please clarify that the heat treatment is carried out for final containers ----------(b)(4)----------.

The sponsor's response: Kedrion confirms that the heat treatment step is carried out on the product in its final container as described in the CMC section provided to FDA in the BLA application dossier and in accordance with 21 CFR 640.81.

Reviewer's comment: the response is acceptable.

Reviewers' comments and IR questions to the sponsor on viral clearance validation (including that from Dr. Mahmood Farshid):

1. Please note that the manufacturing process for plasma-derived products must be validated for its capacity to clear enveloped viruses (HIV, and model viruses for HCV and HBV) by at least two major and independent viral clearance steps. The cumulative log reduction for a given virus should be > 10 logs. Considering these principles, your viral validation studies have not provided acceptable level of virus clearance, and therefore, are incomplete for reasons outlined below:

    - You have overestimated the level of HIV clearance by the precipitation steps. Specifically, "fraction of effluent I to effluent II+ III" and "depth filtration of fraction V suspension" steps are not orthogonal, and therefore the clearance provided by these steps are not additive. Thus, claim of 3.4 $\log_{10}$ clearance for each step for total of (b)(4) for both is an overestimation and must be revised to include log clearance by only one of these steps. Considering these corrections, the total HIV clearance (-(b)(4)-) provided by the precipitation steps (3.4 logs) and that of heat treatment (---(b)(4)---) is less than minimum acceptable level (>10 logs) of clearance for this virus, and therefore, insufficient to provide a reasonable degree assurance regarding the safety of the product with regard to a potential HIV contamination.

    - Please also note that the level of HIV inactivation by terminal heat treatment (--(b)(4)) provided in your validation studies is lower than what has historically been reported for HIV, using this heat treatment. Low initial virus load and limit of the detection of your infectivity assay may have contributed to low clearance demonstrated in your studies. If that is the case, you need to repeat the validation studies to provide more accurate estimate of the capacity of your inactivation step.

The sponsor's responses:

The viral/non viral safety data included in the BLA dossier are the same submitted and discussed during the pre-IND meeting (pre-IND dossier, Module 3.2.A.2 and Module 3.2.R.2 provided on 24th February, 2009 and the pre-IND meeting with CBER of March, 26th 2009) based on which it was stated from FDA at that time "… further validation studies would not be required…" (please refer to page 6 of pre-IND minutes dates April, 8th 2009) and the safety profile of KEDBUMIN was considered acceptable.

Kedrion would like to provide the following considerations/data in order to support the safety of the product with regard to a potential contamination from enveloped viruses (HIV, and model viruses for HCV and HBV).

The two steps investigated
- Fraction of Effluent I to effluent II+III; and
- Depth filtration of Fraction V

---(b)(4)---

----------. Furthermore, as stated in Annex 4 of WHO Technical Report, Series no 924, 2004, ----------(b)(4)----------. This reinforces what is mentioned above that the separation methods can have a different impact on virus removal. Regarding the inactivation of enveloped viruses, it is well known the inactivation occurs during the addition and ----------(b)(4)----------.

Regarding the HIV virus, Kedrion agreed that the low reduction factor observed was due mainly to the low total viral load in the starting material. For this reason, a new validation study for inactivation of HIV during pasteurization step was carried out, and the final results were submitted on April 14, 2011 in final report "Validation of HIV-1 inactivation during the pasteurization step in the purification process of human albumin". The test item was spiked with HIV-1 at defined titer and then subjected to the virus inactivation procedure. Samples were collected from the process before, during and at the end of the process step and analyzed for virus titer by endpoint titration and large volume plating. The $\log_{10}$ reduction factors of 1st run ≥ (b)(4) and 2nd run ≥ (b)(4) were obtained for both after --(b)(4)-- 10 hours of heat treatment.

Reviewer's comments: the responses appear to be adequate.