FOOD AND DRUG ADMINISTRATION

Center For Biologics Evaluation and Research

Memorandum

MEMORANDUM

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Subject: Review of methods/assay validation sections 2.3.P, 2.3.S, and 3.3.S.2 of **STN 125384** Kedrion Biological License Application

To: Crystal Allard, RPM, HFM_380, RPMB, DBA, OBRR, CBER: (301) 827-3927

Action recommended: Approval

Summary: Module 2.3.P of the original BLA STN 125384 for Human Albumin (Kedbumin 25%) contains the following:

Summary Table P.5.1

Tests	**Specifications/Limits**
Character	A slightly viscous liquid, it is almost colorless, yellow, amber, or green
Total protein (g/L)	---(b)(4)---- 235 – 265
pH	---(b)(4)--- 6.4 – 7.4
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 ug/L)	≤ 200
---(b)(4)---	(b)(4)
----------(b)(4)----------	(b)(4)
----------(b)(4)----------	---------(b)(4)----------
Sterility	Sterile
Pyrogens	Pyrogens free
Sodium caprylate (mmol/g proteins)	0.064 – 0.096
N-Acetyl-DL-tryptophan (mmol/g protein)	0.064 – 0.096
------(b)(4)--------	(b)(4)
-------(b)(4)------	(b)(4)
----------(b)(4)----------	---(b)4)---

2.3.P **Drug Product**

Appearance - Test method - Visual Inspection Determination

Validation - Visual Inspection Determination

Identity – Test Method – ---------(b)(4)----------

Validation – ----------(b)(4)----------

Protein Composition Determination – Test Method – -------(b)(4)----------

Validation – ------(b)(4)------

Total Protein Determination – Test Method – --(b)(4)--

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

Total Protein Determination – Test method - --(b)(4)--

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

pH - Test method - pH determination

Validation pH Determination

Sodium and Potassium Determination – Test Method -----(b)(4)-----

Validation – -----(b)(4)-----

Aluminum Determination - Test Method – ---------(b)(4)-

Validation – ----------(b)(4)----------

(b)(4) Determination – Test Method - ----------(b)(4)----------

Validation - ----------(b)(4)----------
-----(b)(4)-------- – Test Method – ----------(b)(4)----------
Validation - ----------(b)(4)----------
Sterility – DMPQ?
Sodium Caprylate Determination – ----------(b)(4)----------
Validation – ----------(b)(4)----------
N-Acetyl Tryptophan Determination Test Method - ----------(b)(4)----
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Validation - ----------(b)(4)----------
---(b)(4)--- Determination – Test Method – ----------(b)(4)-

Validation Determination – ----------(b)(4)-

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

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

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

Pyrogens – Test Method – ----------(b)4)----------
Validation – ----------(b)4)----------
(This test was reviewed by DMPQ)

2.3.P Drug Product

Visual Inspection Determination

Purpose: This test is designed to determine the presence of aggregates in the product by visual determination of color changes that are compared against color standards.

The test is carried out according to the ----------(b)(4)---------- and according to FDA's CFR 21, part 640.82."Methodology and Validation of analytical procedure ICH Q2 (R1)

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

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

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

9 pages redacted (b)(4)

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Pyrogens:

Compendial described in --(b)(4)--
Acceptance: Pyrogen free. Results: Pyrogen free

Reviewer's comment: The method is valid

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

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

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

4 pages redacted (b)(4)

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

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

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

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

Questions

On January 21, 2011 CBER requested additional information from sponsor regarding this submission. This request included:

Question N°10

10. In the section on "accuracy" in summary table P.5-19 of module 2.3.P, please clarify the meaning of "found solutions" in the statement "Assessed on found solutions having different (b)(4) activity."

Kedrion response: Kedrion clarifies that “found solution” is an incorrect translation referring to albumin solutions which contain a ---------(b)(4)---------- lower than the quantitation limit (---(b)(4)------). This means that the solutions have been used as matrix for the addition of a known amount of standard. Kedrion would like to take this opportunity to amend Summary table P.5-19 reporting a more appropriate description of the accuracy test and by correcting the reference of the validation report from MTA-091-R to MTA-092-R (Attachment 5).

Comments: In the sponsors response they promised to provide a revised validation report by the end of February. This document was not received until March 24, 2011. The newly provided information and explanation were found satisfactory.

Question N°11

Comments: Following consultation with the statistical reviewer the following question was submitted.

11. Based on the p-values in the summary table P.5-21, module 2.3.P, you concluded that the ------(b)(4)--------- standards were equivalent. However a calculated p-value greater than 0.05 (or failed to reject null hypothesis) does not imply that the two standards are equivalent. Please provide pre-specified error margins, or equivalence margins used for the equivalence conclusion, if any.

Kedrion response**:**

Kedrion would like to clarify that based on common practice in statistical evaluation for the comparison of regression lines, the overall test for coincidence reported in module 2.3.P does not allow to reject the null hypothesis of coincidence between the two regression lines based on ------(b)(4)--------- standards. This result therefore suggests that the corresponding regression lines do not differ significantly, and therefore can be accepted to be coincident. According to the literature (*1*, *2*, *3*) the coincidence of regression lines is commonly accepted as a way to consider two standards comparable, i.e. providing equivalent results when used. Based on this evidence, Kedrion has not defined any error or equivalence margins. In addition the Standard ----(b)(4)---- was calibrated against the -----(b)(4)----- which was calibrated against the 1st International Standard for ----------(b)(4)----------. The Standard ----(b)(4)---- supply by (b)(4) was calibrated against the 2st International Standard for --------(b)(4)-------- which was calibrated against the 1st International Standard for --------(b)(4)---------. Therefore both ------(b)(4)--------- Standards have as a primary calibration reference standard an International Standard recognized by WHO (------(b)(4)----------) (Attachment 6).

Comments: <u>After further discussion with the statistical reviewer Shiowjen Lee, and the chair the sponsor's response was found satisfactory</u>.

Question N°12

12. In the summary table P.5-19 in module 2.3.P, one could calculate the highest possible excipient concentration, defined as the worst case scenario, as ---(b)(4)--- with Kedbumin containing the upper limit for protein concentration, and the upper limit for excipient concentration, rather than 20 mmol/L of excipients. Please explain this discrepancy and provide data if there was any additional testing done at this upper limit for excipient concentration.

Kedrion response**:**

Kedrion agrees with the comment. An additional test aimed at evaluating the interference of excipients in the finished product on a solution containing sodium caprylate and N-acetyl tryptophan at a worst case concentration of ---(b)(4)--- has been carried. The results are summarized in the following table and show that the excipients do not interfere with the determination of (b)(4) in the finished product.

Parameter	**Acceptance Criteria**	**Results**
Specificity (*vs* Sodium caprylate and N-Acetyl Tryptophan at concentration of ---(b)(4)--)	*1st)* ----(b)(4)---- *2nd)* -------(b)(4)----------	*1st)* ----------(b)(4)---------- *2nd)*---------*(b)(4)*---------- Excipients do not interfere

The revision of the relevant validation report is being translated. Kedrion commits to provide the new revision of the report (MTA-092-R rev 01) by the end of February 2011. The amended summary table P.5-20 reporting the updated results is provided in Attachment 5.

Comments: In the sponsors response they promise to provide a revised validation report by the end of February. This document was not received until March 24, 2011. The sponsor has reported that the changes in excipient concentration were made and they have provided new validation reports that reflect this change.

Question N°14

In assay validation reports for total protein determination, sodium caprylate, ----------(b)(4)---------- rather than only citing "linearity, accuracy and precision.", please also provide validated ranges for each individual method, as was done for the sodium, and potassium ions determination for the drug product, Kedbumin (module 2.3.P summary table P.5-16).

Kedrion response**:**

Kedrion provides the amended Summary Tables P.5-10, P.5-27, P.5-30, P.5-32 and P.5.35 reporting the validated ranges. (Attachment 5).

Comments: The requested changes were made to the specified documents, although it was not clear to this reviewer whether those changes accurately reflected the original intent of my request. I therefore submitted the additional question.

FDA Additional question: Kedrion has provided validated ranges in the results column of the revised summary tables referred to above. Do the values stated for the application range in the results column of the amended summary tables represent the validated range for the assay?

Kedrion response**:**

Kedrion confirms that the application range in the results column of the amended summary tables *P.5.-10, P.5-27, P.5-30, P.5-32 e P.5-35* represent the validated range for the assays.

Question N°15

15. In the table P.5-28 in module 2.3.P that summarizes the assay validation specifications for N-acetyl tryptophan; (b)(4) replicates were reported for accuracy, between run precision and within run precision. Please explain why a minimum of three replicates was not used? Please also provide information for additional replicates.

Kedrion response**:**

Kedrion agrees with the comment. An additional test with three replicates aimed at evaluating the accuracy and between run precision has been carried out. The results are summarized hereafter:

Parameter	**Acceptance criteria**	**Results**
Accuracy	----------(b)(4)----------	----------(b)(4)----------
Between run Precision	-------(b)(4)----- ----------(b)(4)----------	----------(b)(4)---------- ---------- ----------(b)(4)----------

The requested changes were made and the reported procedure included a third replicate was provided.

Review's comment- sponsor's response is acceptable.

Question N°16

16. In the table P.5-30, module 2.3.P the acceptance criteria for (b)(4) determination contains a calculated [-(b)(4)] value. Please explain how the [-(b)(4)] value was calculated, and what the associated error with this value was, and whether samples with (b)(4) and without excipients compared?

Kedrion response**:**

Kedrion clarifies that the calculation has been carried out on the basis of the formula reported on page 140 of the validation report MTA-050-R rev 02, attached to Module 3.2.P.5 of the BLA application. It represents the possible interference of the excipients matrix on routine samples.

Review's comment- sponsor's response is acceptable

Question N°17

17. Attachment P53-13-MTA-050-R pg 21/40 indicates that (b)(4) replicates of (b)(4) samples were measured by this method and compared to "Ordinary samples". Please clarify the term ordinary as it used in this context.

Kedrion response**:**

Kedrion clarifies that "Ordinary Sample" means a sample containing ----------(b)(4)----------. This is a representative value of a routine sample, namely "routinary sample."

Review's comment- sponsor's response is acceptable.

Question N°18

18. In table P.5.16, module 2.3.9 quantitation and detection limits for potassium are given but not for sodium. Please explain why these values are not listed, and please provide this information.

Kedrion response**:**

Kedrion clarifies that potassium is present only in trace amount in the finished product. Sodium is a main component of the product, which specification is 130 –160 mmol/L, therefore "quantitation and detection limits" are not significant parameters to be validated, in accordance to the guideline on the validation of analytical procedures ICH Topic Q 2 (R1): which states that "*The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products*."

Bibliographic References

1. D.G. Kleinbaum, L.L. Kupper and K.E. Muller - Applied regression analysis and other multivariable methods (book) – 2007;
2. S.A. Glantz - Primer of Biostatistics (book, Sixth Edition) - 2005;
3. A.F. Zuluaga, M. Agudelo , C. A. Rodriguez and O. Vesga - Application of microbiological assay to determine pharmaceutical equivalence of generic intravenous antibiotics - BMC Clinical Pharmacology 2009, 9:1

Review's comment- sponsor's response is acceptable.