DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: STN: 125384/0

From: LCDR Sean Byrd, Dir. Reg. Rev. Ofc., OCBQ/DMPQ/MRBI, HFM-675
Yiping Jia, Chair, CBER/OBRR/DH/LBVB

Through: Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/B1, HFM-675
Abdu Alayash, Ph.D., Chief, LBVB/DH/CBER, HFM-343

CC: Lori Peters, CSO/Inspection Lead, OCBQ/DMPQ/MRBI, HFM-675

Applicant: Kedrion, S.p.A.

Product: 25% Human Albumin Solution [KEDBUMIN™]

Subject: **Review Memo** – Review of Responses to Form FDA 483.

Recommendations:

The responses for all observations listed on Form FDA 483 are acceptable.

Background:

Kedrion, S.p.A. (Kedrion) submitted a BLA for their product *Kedbumin* (25% Human Albumin solution) on 3 August 2010. *Kedbumin* is manufactured at their Barga (Lucca), Italy site using albumin paste intermediate manufactured ----------(b)(4)----------. The facility was inspected from 23 February 2011 through 2 March 2011 excluding the weekend. A 4-item Form FDA 483 was issued 2 March 2011. LCDR Byrd (DMPQ) was responsible for reviewing items 1 and 4 and Dr. Jia (OBRR) was responsible for reviewing items 2 and 3.

Review Summary:

Observation 1

You do not have a fully validated visual inspection process for the 100% inspection of filled vials, specifically:

a) **There is minimal assessment for cracks (only --------(b)(4)------ are tested by the ----------(b)(4)---------- test machine);**
b) **There is no assessment for particulates that may be lodged within the beveled region of the stopper of the container/closure system;**
c) **Neither your manual inspectors, nor your automated visual inspection machine, have been assessed for their limit regarding smallest particulate size detection.**

Review of Response for Observation #1 by LCDR Byrd

Kedrion states they will only do a manual 100% visual inspection for product to be sold in the U.S. market. They claim this will allow them to satisfy bullets 1a) and 1b) because their operators are trained to detect defects on the surface and thickness of the glass. This would also include cracks, other glass defects, air bubbles, and sealing issues that could compromise container/closure integrity.

Regarding 1b), Kedrion states that operators are capable of seeing any particulate trapped within the beveled region of the neck and stopper. Furthermore, bottles are incubated for 14 days in a horizontal alignment in accordance with 21 CFR 640.81, which allows for the wetting of the entire stopper and neck region. No microbial growth has ever been detected indicating these types of particulates are not present. The 100% manual visual inspection takes place after the 14 day incubation.

The potential microbial growth between the stopper and the neck of the container is detectable by the trained operators. In fact, containers showing any indication of turbidity or particulates are discarded in accordance with SOP PKG-05-017.

Regarding 1c) Kedrion states the manual visual inspection method has now been validated for the detection of particulates and determined what the smallest particle visible to the inspector is.

A kit of albumin 25% vials was prepared in a laboratory setting, ----------(b)(4)----------. The vials have been added with ----------(b)(4)----------, as described in technical document DCT-413-D-01, of final report DCT-413-R-01.

The aim was to prepare a kit of bottles to be used for assessing the ability of operators to detect particles of different sizes. The validation study is summarized in the attached report VPC-092-R-00. The smallest particulate size detectable by the operators is (b)(4).

Kedrion prepared procedure PKG-05-017 which reports in detail the operative instructions to be followed by the operators during the manual visual inspection for the batches of KEDBUMIN.

Please note that the documents PKG-04-001 and PKG-05-001, mentioned in SOP PKG-05-017 have been already reviewed during the PAI. The other mentioned documents will be available upon request.

Should the BLA be approved, the SOP PKG-05-017 will become effective following the completion of personnel training.

Following that, qualified operators will perform the visual inspection of the three conformance batches of Kedbumin already filled (----------(b)(4)----------), and will follow the same procedure for further batches intended for the US market. Kedrion will record the manual visual inspection and packaging operations on the batch records. The CMC section 3.2.P.3.3 will be revised in order to report only manual visual inspection.

I reviewed the SOP PKG-05-017. All information appears appropriate for detecting and recording defects and has prescribed lighting levels and work/rest cycles adequate to prevent fatigue of the operator. Each operator is only allowed to perform ----------(b)(4)----------.

I reviewed document DCT-413-R revision 01, *Detection Limit Verification of Particulates in Albumin Bottles* and VPC-092-R-00 *Final VPC Summary, Verification of Visual inspection, Visual Inspection Procedure Validation of Albumin with Calibrated Particles.* The study was performed under worst case conditions which included the 50mL bottle with 25% albumin (most viscous.) Contents of the vials were pre-treated to insure extrinsic contaminations were not present. The vials were then artificially contaminated with calibrated particulates in sizes as described above. The kit contained 20 units that complied for no particulates and 20 contaminated units. The contaminated vials contained 1 particle/ 10mL of product. Inspectors were tested on all dosage levels (not just the 50mL size to be sold in the U.S. market.) Results as presented in the validation document appear to support that a trained inspector is capable of detecting particulates down to the (b)(4) size.

The response is acceptable.

Observation 2

The ----------(b)(4)--------- test has not been performed adequately during the last phase of the manufacturing process. The required limit for drug substance should be ----------(b)(4)----------.

Review of Response for Observation #2 by Dr. Jia

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

Reviewer's comment: The response is adequate.

Observation 3

The frequency of the analytical tests specified in the stability program procedure is not adequate as per the current abbreviated stability schedule.

Review of Response for Observation #3 by Dr. Jia

Kedrion concurs with the FDA regarding the stability program. Kedrion has finalized SOP QAS-OS-088 rev 00, relative to the stability protocol specific for albumin intended for the US market, where all time points of the long term stability study at 0, 3, 6, 9, 12, 18, 24 and 36 months have been included, for Kedrion stability programs. The mentioned SOP has been internally approved on April 7th, 2011.

Reviewer's comment: The response is adequate.

Observation 4

The vial wash machine in Room –(b)(4)-, used to wash vials ----------(b)(4)----------, is not fully qualified. Specifically, the machine has not been assessed for its capacity to remove particulate matter.

Review of Response for Observation #4 by LCDR Byrd

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