FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: 8/21/09

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To: File for STN# 125329/0

Through: Dorothy Scott, M.D.; CBER/OBRR/DH/LPD; HFM-345;

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Subject: Final CMC review memo –Bio Product Laboratories IGIV BLA

Product: Immune Globulin Intravenous (Human)
Trade name - Gammaplex®
Manufacturer: Bio Product Laboratories

RECOMMENDATIONS:

This original BLA application is recommended for approval.

BACKGROUND SUMMARY:

Bio Products Laboratory (BPL) submission of this original BLA was received November 17, 2008 requesting U.S.-licensure of a 5% Liquid Immune Globulin Intravenous (Human) product, trade name Gammaplex®. This IGIV product is a modification of the BPL's current IGIV product Vigam Liquid which is licensed in the UK and EU. Gammaplex is manufactured from US derived source plasma, using --------(b)(4)-------- fractionation ----------(b)(4)----------, followed by solvent/detergent incubation, -----(b)(4)----- ion-exchange chromatography, 20 nm nano-filtration, --(b)(4)--, final formulation to bulk drug substance, sterile filtration, final-product filling, with a terminal high temperature/low pH hold on the ----------(b)(4)----------, pH 4.8--(b)(4)-). The final formulation is: --(b)(4)-- protein consisting of ≥95% IgG, -(b)(4)- mM sodium chloride, -(b)(4)- mM glycine, -(b)(4)- mM sorbitol, -(b)(4)- µg/mL polysorbate 80, pH 4.8 – -(b)(4)-. Gammaplex is filled at 50 ml, 100 ml, and 200 ml sizes (2.5 g, 5 g, and 10 g) in Type II glass bottles.

CMC areas reviewed by me for this BLA include Plasma Quality, Plasma Look Back, Analytical Assay Validation, and TSE Clearance studies.

REVIEW SUMMARY:

Plasma Sourcing:

BPL obtains US source plasma from licensed centers operated by --------(b)(4)-------. Some of these suppliers also provide BPL with ------(b)(4)----- plasma for BPL's Rabies Ig, Tetanus Ig, anti-D Ig, and Varicella-Zoster Ig, products which are all licensed in the UK but not distributed in the US. Plasma supplied to BPL is frozen, stored, and transported, under appropriately validated processes. Plasma from the US plasma suppliers is transported to various US warehouses prior to shipment to BPL (----------(b)(4)----------). Plasma may be stored for -----(b)(4)---- prior to shipping to BPL. Transport of US plasma to BPL is routinely done by ---(b)(4)--- but can also be done --(b)(4)-- services. Plasma transport to BPL uses validated contains (-----(b)(4)----) and has been validated for temperature control using temperature monitoring. Prior to fractionation, source plasma is stored at BPL for ----------(b)(4)----------. Frozen plasma can be stored for -----(b)(4)---- prior to use in products manufactured from normal source plasma. However, current operations have been using plasma within much shorter timeframes (--(b)(4)--).

Look Back:

Incoming plasma units are tracked and manufacturing pools are assembled by the ----------(b)(4)----------. This system contains ----------(b)(4)---------- information. Following conclusion of testing units contained in an assembled manufacturing pool are issued a Certificate of Release. At BPL's current scale manufacturing pools are between ---------(b)(4)------- of Plasma (Maximum --(b)(4)--); with the number of donations = -----(b)(4)---- (Maximum --(b)(4)--).

During the PAI in May 2009, I reviewed BPL's procedures and SOPs for follow-up of plasma donor information. All procedures and SOPs were found to acceptable and provided appropriate levels of control for the incoming plasma used in manufacture.

- SOP BPL/00033/05/SOP dated 04/14/2008 "Review of Post-donation Information- US Plasma"
- SOP PDN/00140/06/SOP "Assignment of Plasma to Production Batches and Subsequent Transfer of Plasma to Production" dated 06/23/2008
- SOP PDN/00139/03/SOP dated 06/04/2007 "Action to be taken on Receiving an Incident Report"
- SOP PDN/00164 "Removal of Rejected Material"
- SOP IT/00052/11/SOP "System Security for ----------(b)(4)---------- Software" dated 04/13/2009
- SOP PDN/00135 "Verification of Plasma Bin Contents"
- SOP PDN/00384 "Moving Donations from One Bin to Another"
- SOP PDN/00140 "Assignment of Plasma to Production Batches and Subsequent

Transfer of Plasma to Production"

I also reviewed look back reports for the last 18 months and requested 12 donor deferral reports to ascertain follow up and risk analysis. All the reports were complete with the necessary documentation of risk assessment, donor information updates, and tracking/verification of plasma unit destruction.

The look back departments are located for the suppliers at the following addresses:

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

Reprocessing:

In Section 3.2.P.3.5.22 of the BLA submission BPL proposes to perform recovery and reprocessing of Gammaplex. BPL defines these process steps as:

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

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

This issue resulted in a 3 item IR being sent to BPL on March 18, 2009:

1. Please provide copies of any SOPs related to reprocessing, reworking, or "recovery", of IGIV products or intermediates, which would be applied to your Gammaplex process.
2. Please provide a listing of any reprocessing, reworking, or "recovery" for any lots of Gammaplex (clinical lots, conformance lots, and manufacturing intermediates that are planned for use in Gammaplex manufacturing) that have taken place. Please include details of the events which led up to the reprocessing/reworking/ "recovery", what reprocessing/reworking/"recovery" took place, whether or not any manufacturing deviations were filed, whether any investigations and/or CAPA took place.
3. Please provide specific details of the circumstances for which reprocessing/ reworking/"recovery" is considered acceptable.

In response to #1 BPL provided SOP PDN/00447/rev 03 dated March 16, 2009 "Rework

of Filled Vigam and Gammaplex" which states that Gammaplex is not to be reworked. Also provide by BPL was process validation document PV45400101 "Process Validation Protocol for Reprocessing Gammaplex" dated Sept. 4, 2008. This protocol was discussed extensively with management during the PAI in May, 2009 and they understood the design short-comings and agreed to submit an revised plan to the agency post-approval amendment in order receive any additional re-filtration into the Gammaplex license. For IR question #3 BPL stated that they submitted a formal request to reprocess lot# ---(b)(4)--- (under ----------(b)(4)----------) but that BPL had decided to reject all lots which had undergone reprocessing.

Assay Validation:
BPL assay validation protocols follow ICH, CPMP, and FDA, guidelines for the design and execution of assay validation. Determination of Specificity, Accuracy, Precision, Repeatability, Intermediate Precision, Limit of Detection (LOD), Limit of Quantitation (LOQ), Linearity, Range, Sensitivity, and Robustness, were performed where possible. The studies were appropriately designed and executed for most assays. The validations were deemed acceptable although some assays could have used additional studies (--(b)(4)--) and were the subject of discussion with the BPL Laboratory managers.

Assigned sections included the following Assay Methods:

- Determination of Polysorbate 80
- Determination of ----------(b)(4)---------- concentration
- Determination of ----------(b)(4)----------
- Protein composition by ----------(b)(4)---------- (Purity)
- Determination of --(b)(4)-- Concentration
- Distribution of ----------(b)(4)---------- Method
- Determination of ----------(b)(4)----------
- Determination of total protein by --(b)(4)--
- Determination of neutralizing antibody to Diphtheria
- Determination of neutralizing antibody to Measles

Other analytic methods reviewed but not included in this memo - pH, Conductivity, Total Protein by ---------(b)(4)---------, Total Protein by -(b)(4)-, Determination of Osmolality as all were well established compendial assays.

Determination of Polysorbate 80
The Polysorbate 80 concentration is determined --(b)(4)----------
----------. The resulting extract is measured ----------(b)(4)----------. The assay validation --(b)(4)-- and assay SOP - BPL/QAC/391/rev08 "-----(b)(4)---- Method for the Determination of Polysorbate 80" dated June 16, 2008 were reviewed during the PAI, conducted in May 2009, and both documents were found to be acceptable. The acceptance specification for the stabilizing agent PS80 in final drug product is --(b)(4)-- mg/L.

- Specificity: results of ----------(b)(4)----------

- Accuracy: ----------(b)(4)----------
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3 Pages Determined to be Non-Releasable: (b)(4)

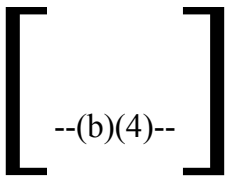
----------(b)(4)----------

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

[--(b)(4)--]

Distribution of ----------(b)(4)----------
---------- **Method**
The -(b)(4)- method was used during Gammaplex product development but has been replaced by the ---(b)(4)--- technique as the method of choice and is compendial
----------(b)(4)----------
---------- Specification, determined by ---(b)(4)---, uses -(b)(4)- as standard reference preparation, with a limit of ----------(b)(4)--------
----------. A --(b)(4)-- limit of -------(b)(4)------- has also been introduced. Identities of -(b)(4)- are determined by comparison with the reference preparation. The assay validation study RDP0061 and the assay SOP – BPL/QAC/00457/rev01 "----------(b)(4)---------- Assay" dated Nov. 19, 2007 were reviewed during the PAI in May 2009.

3 Pages Determined to be Non-Releasable: (b)(4)



Determination of Total Protein by --(b)(4)-- **method:**
-(b)(4)- specification, determined by --(b)(4)-- method, with a limit of ---(b)(4)--- of the quantity stated on the label. Average total protein is -(b)(4)- g/L. Assay validation study RDP0039 and SOP QAC/00357 rev 13 dated Feb 02, 2008 were reviewed during the PAI in May, 2009.

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

Diphtheria *in vivo* Assay Standard
CBER antitoxin reference preparation F4507-31 is currently used. This testing was performed as per -------(b)(4)------- by the ----------(b)(4)---------- ---------- which has ISO 17025 accreditation. Tests were internally validated according to ----------(b)(4)----------.

Measles *in vitro* Neutralization Assay Standard
CBER reference preparation lot 176 was used for the data submitted in this CTD, with a ratio limit acceptance criterion of --(b)(4)-- of sample standard (for a -(b)(4)- preparation =-(b)(4)- X CBER Standard 176). Test is performed under contract by --(b)(4)-- and the validation protocol CP-2532 "Validation of the Measles Antibody Potency Test of 5% Globulin Intravenous" done with 3 lots of IGIV (----------(b)(4)----------) was reviewed and found acceptable.

BPL Gammaplex TSE Clearance Studies:

The supplied BLA contained a number of validated TSE clearance studies. The model consisted of spiking with a ----------(b)(4)---------- (strain -(b)(4)-) in a scaled down versions of the various large-scale production processes. --(b)(4)-- assays for -(b)(4)- were done on samples of the ----------(b)(4)---------- ----------. The studies performed for validating TSE removal were appropriately designed and carried out by BPL and ----(b)(4)----, the TSE clearance values provided by these studies appear to be in ranges that are lower than expected. The

fact that these studies were done using only ------(b)(4)------ precludes the inclusion of any TSE clearance claims in Gammaplex labeling. However, since BPL has used only US source plasma for the last 11 years the risks of including TSE contaminated plasma in their manufacturing stream are substantially reduced.

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

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

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

These studies covered the following manufacturing process steps and indicated the following capacities to remove the scrapie agent:

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

[--(b)(4)--]

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

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[--(b)(4)--]

CONCLUSIONS:

BPL has performed adequate analytical assay validation, plasma safety and quality control measures, submitted sufficient documentation in their BLA, that I would recommend that this license application be approved.