M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

TO: STN: 125329/0 Immune Globulin Intravenous (IgG) (Human), Gammaplex®, Bio Products Laboratory (BPL)

FROM: James Crim, Review Biologist, CBER/OCBQ/DMPQ/MRB2, HFM-676

SUBJECT: Final Review Memo – CMC/DMPQ Review of Bio Products Laboratory's (BPL) original Biologics License Application (BLA) for Immune Globulin Intravenous (IgG) (Human), Gammaplex®.

THROUGH: Chiang Syin, Ph.D., Branch Chief, DMPQ, MRB II, HFM-676

RECOMMENED ACTION:

Recommend approval of Bio Products Laboratory's (BPL) original Biologics License Application (BLA) for Immune Globulin Intravenous (IgG) (Human), Gammaplex®.

EXECUTIVE SUMMARY:

A Pre Licensing Inspection was performed for this BLA (STN: 125329/0). The facility information is as follows**:**

Bio Products Laboratory (BPL)
Dagger Lane
Elstree
Hertfordshire
WD6 3BX
United Kingdom
FEI: 1000184635

A summary of the activity at this address is as follows: Fractionation start pool virology testing is performed on the drug substance by BPL. Manufacturing, release and stability testing of the drug product are performed by BPL or their approved contract laboratory.

The BPL facility was inspected on May 15, 2009 through May 22, 2009. A Form FDA 483 was issued at the conclusion of the Pre Licensing Inspection. The compliance outcome was Voluntary Action Indicated.

BACKGROUND:

Final Drug Product:

Gammaplex is supplied as a sterile liquid (clear, colorless sterile solution): one bottle of the 5 g dose contains 100 mL of a 50g/L (-(b)(4)-) IgG solution. The 2.5 g dose contains 50 mL of 50g/L (--(b)(4)--) IgG solution and the 10 g dose contains 200 mL (--(b)(4)--) of the same IgG solution. Quantities of inactive ingredients vary depending on dose, and include; Sorbitol, Glycine, Sodium Chloride, Sodium Acetate, Polysorbate 80, and Water for Injection (WFI).

Facility information:

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Activity: Fractionation start pool virology testing is performed on the drug substance by BPL. Manufacturing, release and stability testing of the drug product are performed by BPL or their approved contract laboratory.

The BPL facility was inspected in May 15 – 22, 2009. The outcome was Voluntary Action Indicated.

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

Activity: The virology testing of individual donations is performed on the drug substance by ---------(b)(4)----------

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

Activity: The virology testing of individual donations is performed on the drug substance by ---------(b)(4)----------

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

Activity: Fractionation start pool virology testing is performed on the drug substance by -(b)(4)-. Nucleic Acid Amplification Testing (NAT) testing is performed on the drug product by -(b)(4)-.

REVIEW:

Manufacturing

BPL provides the Manufacturing of Drug Product as follows:

Drug Substance:

Plasma is obtained from suppliers who are members of the Plasma Protein Therapeutics Association (PPTA). Donor centers which have been licensed by the FDA are used in the manufacturing. Donor screening includes HBsAg, anti-HCV, anti-HIV 1+2, HCV-RNA, HBV-DNA, HAV-RNA, B19, and HIV-RNA.

The ----------(b)(4)----------
---------- Method is used and read ----------(b)(4)----------.

The following Biological Safety Tests are performed on Gammaplex 2.5g (50 mL), 5g (100 mL) and 10g (200 mL) dose sizes:

- Sterility (Limit: pass) compliance reference is ----(b)(4)----.
- Pyrogenicity ◦C/n rabbits (limit: pass) compliance reference ----(b)(4)----.
- Endotoxin (-(b)(4)-), EU/mL (Limit -(b)(4)-) compliance reference --(b)(4)--.
- General Safety Test (Limit: pass) compliance reference 21 CFR 610.11

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

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

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

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

Containers used in Gammaplex

The 50 mL, 100 mL or 250 mL glass infusion bottles (----------(b)(4)----------) are uncolored type II glass. The stopper is a -(b)(4)- mm stopper (----------(b)(4)----------), made of --(b)(4)-- rubber which conforms to the type I closures. The flip off seal is made of ----------(b)(4)---------- nm white) supplied by -(b)(4)-.

BPL provides the following two letters of cross reference for the container closure (stoppers and vials):

- Drug Master File ----------(b)(4)----------, for the -(b)(4)- Type II glass vials (50ml, 100ml and 250ml) from ----------(b)(4)----------,

- Drug Master File ----------(b)(4)----------, for the -------(b)(4)---------- from ----------(b)(4)----------.

Container Closure Validation

Gammaplex is filled on the --------(b)(4)-------- filling line comprising several components including a bottle ----------(b)(4)----------, filler and oversealer. The container closure process overview starts with --(b)(4)----------
----

Closure components

The analysis of Filling Line -------(b)(4)--------- overseal Head Pressure data from -(b)(4)- batches of --(b)(4)--, which is identical to the Gammaplex filling arrangements, showed the overseal head pressure control system produces overseal applied within a very narrow range of pressure (Mean overseal Head pressure: --------(b)(4)--------). Measured in Newtons (N=Newtons).

Bacteriological Challenge of the container/closure system a total of --(b)(4)-- mL bottles were filled with -(b)(4)-. The vials sere ------------------------(b)(4)------------------------- -- -- -- -- ---

The container closure integrity using a bacteriological challenge was repeated using ----------(b)(4)----------. The study is described below.

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

BPL reports no positive results were demonstrated and all positive controls failed as expected.

BPL states there was no provision for -(b)(4)- circulation. BPL state it is was not possible to create --(b)(4)-- in the instance to monitor the behavior of the -(b)(4)- leaks in

the bottles. -----------------------------------(b)(4)---------------------------- was used to create the positive controls. BPL states the detection was considered to be sensitive enough to detect leaking bottles with leaks equivalent to a -----------(b)(4)--------------.

New Container Closure/Integrity Data

During the PLI (Pre Licensing Inspection) the first observation detailed the fact that the new method of a -------(b)(4)------- test, the secondary method BPL uses for their Container/Closure Integrity testing has not been performed. The -(b)(4)- Method is BPL's primary test method for container closure integrity on the final product container.

---(b)(4)--

The -------(b)(4)------- study results showed all acceptance criteria were met. All vials passed no visible turbidity parameter. The positive controls were turbid and the negative controls showed no turbidity visible. In addition, the growth promotion properties of the media in test vials post container closure integrity test were satisfactory.

Compatibility with Bottle and Closures

BPL states the compatibility of Gammaplex with the rubber vial stopper and bottle has been studied throughout the Gammaplex stability trial. All bottles are held in ----(b)(4)------------- to ensure direct -------------------(b)(4)----------------------. The bottles are held at ---------------(b)(4)----------------------- and tested at regular intervals for key stability indicators. All bottles entered into the trial are taken from batches manufactured at

-(b)(4)- production scale and cover 2.5g, 5g and 10g fills into type II glass sealed with --(b)(4)---- rubber stopper adhering to the chemical requirements for -(b)(4)- closures. The stability data for all Gammaplex batches is provided for the Product Reviewer in section 3.2.P.8.

BPL states the compatibility of Gammaplex using the wide range of test methods. The methods used in the compatibility studies include the following:

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

BPL states each method type was filled with -(b)(4)- mL of Gammaplex and a determination of -----(b)(4)---- extractables, additional sets were filled with -(b)(4)- using the same method stored under the same conditions. The result from these studies confirms the compatibility of Gammaplex with a range of giving method.

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

I note the --(b)(4)-- extractable testing was done by a contract testing lab -------(b)(4)----------.

The results of this study showed no significant differences between the control sample held in the ----------(b)(4)---------- and compatible with Gammaplex final drug product.

Manufacturing

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

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

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

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

--(b)(4)--

--(b)(4)--

--(b)(4)---

Inspection, labeling and Packaging

The liquid product is incubated at -----------(b)(4)------------- and then visually inspected for gross defects (e.g. discoloration, damage to overseal) and for evidence of microbiological contamination (e.g. turbidity, particles). The bottles are labeled by machine. Variable data is overprinted at the time of labeling, including expiry date and batch number. Bottles are packed in cartons with a leaflet and sling. Product is stored in quarantine --------(b)(4)-------- before release.

Computer Controlled Process Steps

BPL states the following computer control systems are utilized in the manufacturing of Gammaplex:

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

Other Plasma Derived Products Processed in Same Areas and Shared Equipment

Cleaning and changeover was reviewed during the Prior Approval Inspection.

BPL states several other products are processed in the same fractionation room, --(b)(4)----------, are all process in the same room as Gammaplex. The --(b)(4)-- are shared, as well as the -(b)(4)- units that clean the --(b)(4)--. Fractionation of ----------(b)(4)---------- uses the same equipment as Gammaplex. From --(b)(4)-- onwards, the equipment is shared with ---------(b)(4)---------, and the rooms are common processing areas as well. BPL states -----(b)(4)---- IgG products may also be processed in the same rooms but the equipment is not shared with Gammaplex.

Cleaning and Sterilization

The detergents used in manual cleaning within the manufacturing area are either -(b)(4)- detergents such as --(b)(4)-- or ---------(b)(4)---------- such as ---------(b)(4)---------.

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

BPL states ----(b)(4)---- are disassemble and washed in --(b)(4)-- rinsed in ------(b)(4)----------.

Vessels and Pipe Lines

BPL states all vessels and pipe lines are made of ----------(b)(4)---------- and cleaning ----------(b)(4)---------- system.

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

This vessel is disassembled and washed with --(b)(4)--, rinsed in ----------(b)(4)----------

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

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

-----(b)(4)---- Filter Housing (-(b)(4)- filtration)

The filter housing and all associated pipework is made of ----------(b)(4)---------- and are cleaned ----------(b)(4)----------.

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

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

----(b)(4)---- Sterilizing Filters

BPL states the ----(b)(4)---- sterilizing filters are disassembled, the housing cleaned in ----------(b)(4)----------. Next, they are reassembled with new filter, flushed with -(b)(4)- and integrity tested after sterilization in the autoclave.

The validation for the sterilization was reviewed during the pre licensing inspection (PLI).

Stoppers for Bottles

The stoppers are sterilized by ----(b)(4)--. The validation for the sterilization was reviewed during the PLI.

Bottles

The bottles are sterilized by --(b)(4)--. The validation for the sterilization was reviewed during the PLI.

Use/Storage of ----------(b)(4)----------

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

---(b)(4)--

Process Validation

Compatibility of ----------------(b)(4)-----------------

--(b)(4)---

Qualification of Critical Gammaplex processing equipment and filling

BPL states the cleaning validation of product contact equipment which is not dedicated to Gammaplex and also the qualification of safety critical equipment which impacts directly on the sterility of the final product is included in the media fill validations and revalidation of the sterilization (Autoclave) and depyrogenation tunnel.

Other items included in the submission are the following:

- Validation of Services (steam, WFI)
- Description and drawing of the Viral Secure Area (VSA)
- Sterilization Filter Validation
- Shipping Studies for the transport of drug product to the USA.

Compatibility of ------------------------(b)(4)------------------------

--(b)(4)---

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

Compatibility of solvent --------------------(b)(4)-----------------

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

Cytotoxicity of filter extracts

BPL reports samples tested were:

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

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

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

Qualification of Critical Gammaplex Process Equipment and Filling

BPL states equipment used for the cleaning and sterilization of Gammaplex process equipment includes autoclaves, dry heat bottle depyrogenation tunnels and stopper washers, equipment washing machines and (b)(4) systems. BPL states a risk assessment was completed for the Gammaplex manufacturing process. This evaluation identified the stages of manufacture with the greatest degree of risk of failure, providing a rationale for critical validation. The following critical stages have information on the qualification:

1. Cleaning
2. Sterilization
3. Filling

Cleaning
BPL uses a --(b)(4)-- approach to cleaning validation. Related products are grouped together and cleaning processes validated after equipment is soiled with "worst case" products intermediates. --(b)(4)-- consecutive applications of the cleaning procedure are performed and shown to be successful in order to prove the method is validated. For cleaning procedures for products and processes, which are similar, it is considered acceptable to select a representative range of similar products and processes. BPL provides a table of the acceptance criteria used to measure the effectiveness of cleaning during validation.

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

Automated equipment washer

BPL states the automated equipment washer is used to clean ---(b)(4)--- equipment prior to --------(b)(4)-------. This machine uses ------(b)(4)----- washes followed by ---(b)(4)----------. The machine has been qualified to demonstrate clearance of cleaning agents and cleaning to acceptable microbiological levels of a ----------(b)(4)----------.

The validation data was reviewed during the Pre Licensing Inspection.

Sanitization by ----------(b)(4)--------- systems

-(b)(4)- units are installed throughout the production area and operate on the general principle:

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

Steam Sterilization and Depyrogenation

BPL states the sterilization equipment used in the Gammaplex process is routinely revalidated against dedicated standard operation procedures. Autoclaves are maintained and loads are requalified at appropriate intervals. Autoclave loads are routinely requalified, thermometrically to demonstrate that the autoclave is sterilizing the load concerned. In addition, the accuracy of the test thermocouples is check against standard -(b)(4)- at the expected temperature range of the autoclave. Leak rate tests are performed ----------(b)(4)----------. Air detector function and performance tests are carried out to confirm the leakage rates necessary to cause the air detector to pass and fail a cycle. A standard load is run (-----(b)(4)-------), to compare autoclave performance with the previous requalifications. As a minimum, BPL states a selection of production loads are tested on the --(b)(4)-- load cycle.

Steam sterilization using Biological Indicators (BIs)

BPL states the sterilization process is based upon an --(b)(4)-- cycle, although, under normal operating conditions, it is reasonable to expect the load bio burden to be minimal. The critical parameters are: ----------(b)(4)----------
---

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

Dry Heat Depyrogenation Tunnel

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

Validation of the --(b)(4)-- Depyrogenation Tunnel

BPL states -(b)(4)- endotoxin reduction runs were carried out. This means that the tunnel was configured so that the bottles were subjected to temperatures and times below what is normally achieved during routine production in order to provide the retest challenge for Endotoxin reduction.

All -(b)(4)- tests gave in excess of a -(b)(4)- $\log_{10}$ reduction in endotoxin, successfully exceeding the acceptance criteria of a -(b)(4)- $\log_{10}$ reduction. All bottles contained -(b)(4)- thermocouples. All -(b)(4)- tests had negative controls. The run dates were June 24, 25 and 26, 2008.

Validation of Filter integrity

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

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

The validation data along with the batch record was reviewed during the Pre Licensing Inspection.

Validation of Aseptic Filling

The filling line was installed in 1994, and has been in routine production use at BPL. The line is located in the manufacturing ----------(b)(4)----------
---.

The filling line consists of the following equipment:

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

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

Media Fill

One media fill (batch ID number -(b)(4)-) of -(b)(4)- bottles (-(b)(4)- mL) was performed.

The following aseptic operations were carried out during the media fill:

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

BPL provides a final product review for Vigam liquid for the period of July 2001 to July 2004 and a review of the media fills performed on this line from 1999 to 2004.

Validation of Utilities

The validation along with a review of the trending data of each utility was reviewed during the Prior Approval Inspection.

Water for Injection

BPL states the sampling of the WFI bulk water storage tanks is performed on a regular --(b)(4)-- basis. Sampling of all user points, in the distribution system, is performed on a --(b)(4)-- basis.

The samples are taken aseptically, inspected visually for particulate content, then subjected to testing for endotoxin (-(b)(4)-) and for total viable counts (target level – (b)(4)-, action level --(b)(4)--). BPL states the WFI bulk water generator has a facility for automatic shut-down if the conductivity of the distillate exceeds -(b)(4)- micro Siemens.

Demineralized/Purified Water

Microbial counts are monitored routinely as follows:
----------(b)(4)----------

Microbial counts are also carried out from water taken from sampling points within the distribution system, on a rotational basis so all points are sampled within a --(b)(4)-- period.

All samples are stored at ---(b)(4)--- while waiting for processing and for ------(b)(4)------ between collection and --(b)(4)-- of the sample. A sample of the specified volume is ----------(b)(4)----------.

Compressed Air

BPL states compressed air is filtered at ----------(b)(4)---------- filter.

Clean Steam

Clean steam is generated by -(b)(4)- clean steam generators. ---(b)(4)--- water at less than --(b)(4)-- conductivity is fed into the generator. The steam is monitored at -(b)(4)- -(b)(4)-- intervals for dryness and content of -----(b)(4)---- gases. The Steam Dryness Value (D), according to BPL, should be within ---------(b)(4)---------. The sample is collected by a ----------(b)(4)---------- gases are measured by sampling steam from a sample discharge valve.

The Viral Secure Area (VSA)

At BPL, the VSA is an ISO 14644-1 Grade -(b)(4)- area, with a dedicated air supply. The VSA is supplied with HEPA filtered air by -(b)(4)- Air Handling Units, which maintain a minimum of ----(b)(4)---- to adjacent or non-VSA processing area. The

pressure differential is monitored and recorded with alarm on failure of an Air Handling Unit. BPL provides a figure (Figure no. 1) detailing the arrangement.

BPL states entry into the VSA of people, equipment and materials is strictly controlled by authorized procedures. There is a dedicated change area for personnel to enter and exit the VSA.

Design

The VSA is located in Building -(b)(4)-; the manufacturing section of BPL is shown on Figure no. 2. -(b)(4)- interlocked airlocks join the VSA to the routine processing area. ----------(b)(4)----------. Personnel access the VSA via the dedicated changing room, -(b)(4)-. Supplies used within the VSA are transferred using dedicated airlock -(b)(4)-.

Validation of Aseptic Filling Environment

The filling area is supplied with HEPA filtered air and Aseptic filling rooms are classified as grade -(b)(4)-. BPL states dynamic in-processing monitoring is performed. In operation, a ----------(b)(4)---------- area for particle detection at a ----------(b)(4)----------.

A --(b)(4)-- is used during the smoke challenge tests of HEPA filters. The --(b)(4)-- smoke challenged is adjusted to give the desired reading on the --(b)(4)--, usually between --(b)(4)--. The --(b)(4)-- side of the filter is then ----------(b)(4)---------- to detect leaks.

Smoke is generated --(b)(4)-- of the HEPA filter, ---(b)(4)--- measured and measured again --(b)(4)-- of the filter, once the air flow is checked for the correct flow.

Air flow velocity measurement

BPL states the air flow velocity is measured by either a ----------(b)(4)----------, depending on the size of the filter face.

Filter Validation

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

The same type of sterilizing filter is used -------(b)(4)-------. The validation studies performed by the filter supplier as follows:

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

Physicochemical properties of the Gammaplex formulation are described by BPL and include concentration in parenthesis:

- Immunoglobulin (50 g/L)
- Sorbitol (50 g/L)
- Sodium Chloride (40 mM)
- Sodium Acetate (20 mM)
- Glycine (70 mM)
- Polysorbate 80 (--(b)(4)-- mg/L)
- pH (4.9)
- --(b)(4)----------
- --(b)(4)----------
- --(b)(4)----------
- --(b)(4)----------

Sterilizing Filtration Process and Parameters

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

Virus Secure Area Operations

Final formulation of the product is completed in the VSA after the conclusion of the -----(b)(4)---- process. The product ----------(b)(4)----------
---

Preparations of filters for use in the Aseptic Filling Suite

BPL states the preparation of the filter --(b)(4)-- involves flushing the -(b)(4)- at --(b)(4)---------- for a minimum of --(b)(4)-- until the ------(b)(4)------- of the filtrate is --(b)(4)----------.

Sterilizing Filter Validation Summary

The following studies were performed for the sterilizing filter validation:

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

I note that Gammaplex was formerly called Vigam Sorbitol.

On May 1, 2009 BPL submitted an amendment to the BLA to redefine the sterilizing filter. The manufacturing process involves -(b)(4)- sterilizing grade steps: ----(b)(4)------
---

----------. The same validation was performed as stated above. The redefinition does not constitute a change in the process and the contact time with the filters has not increased only the definition of the sterilizing filter has been changed.

The following sterilizing filter validation is provided in the May 1, 2009 submission:

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

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

Filter integrity testing

BPL states the after completion of the aseptic filling operation, the filter is flushed with -(b)(4)- at ----(b)(4)---- until the conductivity of the filtrate is ----------(b)(4)----------. The filter is ten subject to forward flow integrity testing. The integrity test parameters used for the --(b)(4)-- are as follows:

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

The ----------(b)(4)----------, while subject to --(b)(4)-- flushing and sterilization procedures, is not subject to integrity testing at ----------(b)(4)----------

Sterilization of filters for use in aseptic processing

The sterilizing cycle consists of air removal stages, a sterilization hold period of --(b)(4)--
---

The validation data was reviewed during the PLI.

Recovery and Reprocessing of Gammaplex

BPL defines both recovery and reprocessing. Recovery is ----------(b)(4)----------
---
---------- Reprocessing refers to ----------(b)(4)----------

----------.

BPL provides a number of batches covering the range of presentation sized were filled from the same bulk formulated product to support potential delays to filling and refiltration of bulk product.

The defined conditions for recovery of bulk product are as follows:

- Maximum number of filtrations (-------(b)(4)-------) post formulation: -(b)(4)-
- Maximum storage time of bulk product prior to filling: --(b)(4)--
- Storage temperature prior to filling: --(b)(4)--

Criteria for Reprocessing Gammaplex

BPL provides the criteria for reprocessing based on the following:

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

Non-compliant drug product will only be reprocessed for the following reasons:

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

Validation of reprocessing has not been specifically undertaken for Gammaplex and BPL proposed to perform concurrent validation on batches undergoing reprocessing and provide comparability data demonstrating equivalence of reprocessed batches and with routine product. Stability studies will also be performed.

BPL provides a summary comparability Protocol including the specification tests and a range of additional non-specification in Appendix 1.

Non-Viral adventitious agents are provided in the index.

Control of mycoplasma, bacteria, and fungi are controlled with procedures. Raw materials are tested for ------(b)(4)-------. All bulk chemical used in the manufacturing of Gammaplex are microbiologically tested at BPL or the supplier. Lots containing --(b)(4)---- are rejected.

According to BPL plasma is obtained from suppliers who are members of the Plasma Protein Therapeutics Association (PPTA). Only donor centers which have been licensed by the FDA are used. All equipment used in manufacturing is cleaned with ----(b)(4)---------- as part of the cleaning and change over for non dedicated equipment.

Plasma is purchased from approved suppliers in the US according to FDA guidelines.

Transport Validation for Shipment of Gammaplex Drug Product (Shipping Validation)

BPL states that Gammaplex is a reformulation of an existing BPL IGIV product and has completed clinical trials in the USA for treatment of Primary Immunodeficiency. The product was dispatched to ---------(b)(4)---------, USA by BPL.

All product was in the standard, sealed 100 mL bottle, applicable to Gammaplex. ---------(b)(4)----------. Dataloggers were placed ------(b)(4)---------, to mimic a worst case area in terms of temperature changes.

A total of -(b)(4)- shipments (with a minimum of -(b)(4)- bottles shipped) of Gammaplex were sent to the USA for use in the clinical trial. BPL shows a table, (page 1659, volume 5) detailing the maximum and minimum temperatures recorded during each of the -(b)(4)- shipments. The temperature acceptance criteria specified for shipments of Gammaplex to the USA was --(b)(4)--. The claimed storage temperature range for Gammaplex is +2 °C to +25°C.

The milestone times detailed were:

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

BPL reports two deviations one during the October 10, 2005 shipment and one during the October 16, 2006 shipment. The minimum temperature recorded during transportation fell below the average of --(b)(4)--. BPL states the most likely cause of the temperature deviation was determined to be that the summer packing configuration for the thermal container was used and this may have caused the slightly reduced temperature recorded. For the following shipment, the winter packing configuration was used and all temperatures recorded were within the specified acceptance criteria. Stability studies data indicated that there was no adverse impact to the product by the temperature recorded, and the decision was made to release the shipments for use in the clinical trial.

Container Closure System

Containers

Made from uncolored --(b)(4)-- glass treated with -----(b)(4)------- to give a ---(b)(4)--- ---------- with conforms to the -----(b)(4)---- test for type II glass.

Bottles are several sizes:

- 68 L brimful (50 mL fill size)
- 125 ml brimful (100 mL fill size)

- 308 brimful (250 mL fill size)

BPL states a Certificate of Conformance for each delivery is supplied by the manufacturer with regard to ----------(b)(4)---------- extraction levels. In addition, -(b)(4)- delivery of bottles is sampled, the glass check for conformance with -(b)(4)- And physical checks (Critical dimensions, cracks, chips, bubbles and foreign bodies, etc.).

Stoppers

This is a ----------(b)(4)---------- diameter, --(b)(4)-- rubber, stopper conforming to -(b)(4)-. BPL states a Certificate of Conformance for each delivery is supplied by the manufacturer which confirms the rubber formulation meets the chemical test requirements for -(b)(4)-. In addition, each delivery of stoppers is sampled and tested as follows:

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

Flip off overseal

This is a ----------(b)(4)---------- with a snap-off ----(b)(4)---- cap.

Control of other Materials

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

Environmental Impact Assessment

BPL states Gammaplex is a human biologic and is excluded from this assessment under CFR 25.31 (c). It is a human immunoglobulin product naturally occurring in all humans

and any administered Gammaplex will be metabolized and excreted in the same manner as any of the patients own material. I agree with the request for categorical exclusion under 25.31 (c).

Facilities and Equipment

BPL manufactures stores and distributes a range of therapeutic products derived from human plasma. The three main product groups manufactured are Coagulation Factors, Immunoglobulins and Albumins. BPL states all products are finished under aseptic conditions. Primary packaging components are sterilized by thermal means (autoclave, depyrogenation tunnel) and each product by filtration. The products and their components are then assembled aseptically.

BPL states all products undergo viral inactivation/removal.

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

BPL's manufacturing facility on the Elstree site was opened in 1988. It has --(b)(4)----
---

--- BPL provides the Gammaplex Flow of Materials -(b)(4)-, Personnel, and waste. The flow diagrams provided were reviewed during the PLI.

Specific Systems

Water Systems

BPL states the water source (potable) water is supplied by pressurized main from commercial company over a wide distribution network. Water is supplied under the Water Supply Regulations 1989.

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

The Potable water is buffered on site in a ---(b)(4)----. This water is ----------(b)(4)--------
--- is produced a -------(b)(4)--------
---------- and fed to user-points. A --(b)(4)-- is installed to minimized bioburden. The system is periodically --(b)(4)-- sanitized.

Replacement of -(b)(4)- water with Purified Water

BPL states the -(b)(4)- water is due to be replaced by PW for GMP issues. The water processing consists of filtration, softeners, reverse osmosis and continuous electron-deionization unites ----------(b)(4)---------- supply -(b)(4)- distribution

Continuous -(b)(4)- sanitization is applied to the tanks. ----------(b)(4)---------- confine the -(b)(4)- to the tanks except when the loops are periodically sanitized. The tanks and loops are maintained at -(b)(4)-. When there is a requirement for higher temperatures, heat exchangers at outlets are used. This system will have -(b)(4)- user-points.

This system is currently being commissioned. BPL states the validated system will be brought into use in stages during 2009.

Water for Injection (WFI)

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

Water Usage

BPL states WFI is used for all processing activities, including ----------(b)(4)---------- of intermediates and make-up of --(b)(4)--. WFI is also used for all product contact equipment --(b)(4)--. WFI is used for ----------(b)(4)----------
---. In bulk production areas, -(b)(4)- water is used for washing and initial rinsing of product contact equipment. -(b)(4)- water is used for the production of WFI and clean steam.

BPL provides a summary of IQ/OQ/PQ validations. The PQ consisted of --(b)(4)-- of monitoring water quality. For the first months all user points were sampled daily for TVAC (Total Viable Aerobic Counts) and BET (Bacterial Endotoxin). For the remainder of the year all user points were sampled --(b)(4)-- in rotation for TVAC and BET. The action levels for TVAC are --(b)(4)-- and for BET the action level is -------(b)(4)----------
---. BPL states during the validation of the -(b)(4)- phases an OOS TOC event occurred. The TOC rapidly climbed to 1800ppb. The cause of the event was traced to a TOC spike in the town's water supply, which overloaded the --(b)(4)-- system and stills. The spike was short lived, and appeared to be an anomaly. The systems were cleared by flushing. When the PW system is brought into service the -(b)(4)- system will prevent carryover of TOC from any future similar event.

Routine Monitoring of Water Systems

For -(b)(4)- for -(b)(4)- outlets, BET for supplies to ----------(b)(4)----------. Plant room samples --(b)(4)--, outlets sampled in --(b)(4)-- rotation. Conductivity is monitored --(b)(4)--.

Alert and Action Limits

-(b)(4)-

WFI

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

A BPL state for microbiology results, ----(b)(4)----- above warning or --(b)(4)-- action, the outlet is quarantined. An investigation is performed and risk assessment of any potential impact is performed. For the WFI system, conductivity and TOC are monitored --(b)(4)--, if the action limit is exceeded a system alarm is raised and on the new phases outlets are blocked automatically.

BPL provides a diagram of the entire WFI system.

Heating, Ventilation and Air Conditioning (HVAC)

Air is circulated through each room in the Gammaplex process areas in -(b)(4)-. Air Handling Units (AHU) consist of ----------(b)(4)----------. The AHUs are equipped with fresh air volume sensors, exhaust air volume sensors, and supply air volume sensor and extract air volume sensors. HEPA filters used in all classified room are of the following standard ----------(b)(4)----------
----------. The filter frame construction is of --(b)(4)-- or -------(b)(4)----- in order to avoid the shedding of particles.

For containment features the Differential Pressure are monitored for critical areas via continuous computer controlled monitoring systems. IQ/OQ/PQ summaries are provided. The PQ consisted of qualification and test instruments, ----------(b)(4)----------
---

The AHU which supply air to the aseptic filling suite is re-qualified at -(b)(4)- monthly intervals (----------(b)(4)----------) the remainders are qualified on --(b)(4)-- basis.

The re-qualification tests include the following:

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

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

Viable monitoring in the Building -(b)(4)- aseptic fill suite is performed and microbiological and particulate monitoring during all batch fills and filtration. The transfer and filtration of product from production; set up of filling machine and connection to the machine is microbiologically monitored.

The types of samples take in the filling room must be as follows during the filling operation.

i) Passive Air – sampling settle plates
ii) Active Air
iii) Finger plates

Every room in the aseptic filling suite is monitored in dynamic conditions.

Regional Information

BPL provides a listing of batch documentation used in the manufacture of Gammaplex. BPL provides an overview of batch documentation used in the manufacture of Gammaplex batch --(b)(4)-- (5g dose, 20 nm virus filter, plasma pool intermediate batch number ----(b)(4)-------).

Amendment to the BLA

BPL submitted on March 20, 2009 a response to questions from an information request letter dated March 10, 2009. The questions in the March 10, 2009 letter that are specific to DMPQ included the following:

1. A list of alert and action limits for bioburden and endotoxin during the manufacturing process.

2. Please provide a list of hold times and temperatures.

3. Please provide a deviation handling SOP and a list of deviations for the two conformance lots.

4. Please provide a list of the lot release specifications.

5. Please provide copies of any SOPS related to reprocessing and/or reworking of IGIV products or intermediates, which would be applied to the Gammaplex process.

BPL provides bioburden and endotoxin alert and action limits in tabular form for the manufacturing process. The bioburden levels occur at the following steps: ----(b)(4)---
---

---------- The Endotoxin limits occur at the ----------(b)(4)----------
---------- steps. The alert and action levels are based on historical data and appear appropriate.

BPL also provided the qualified hold times and temperatures for the Gammaplex process intermediates below.

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

The following Biological Safety Tests are performed on the Final Drug Product for Gammaplex at the 2.5g, 5.0g and 10g doses: Sterility (-(b)(4)-), Pyrogenicity (temperature [°C] in rabbits), Endotoxin (--(b)(4)-- EU/mL per -(b)(4)-).

REVIEW COMMENTS:

Recommend approval of Bio Products Laboratory's (BPL) original Biologics License Application (BLA) for Immune Globulin Intravenous (IgG) (Human), Gammaplex®.

Prepared by: J.Crim: 1/12/09; 1/13/09; 1/15/09; 1/26/09; 1/27/09; 2/4/09; 4/1/09; 4/10/09; 4/14/09:5/8/09:5/11/09:5/26/09:6/15/09:6/17/09:7/1/09; 7/6/09: 7/1709:8/10/09: 8/13/09; 8/31/09

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