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

Date: August 25, 2009

To: To File (BLA STN 125329/0)

From: Douglas Frazier, Biologist, HFM-345

Through: Dorothy Scott, Chief, DH/PDL, HFM-345

CC: Debra Cordaro, RPM, HFM-370

Applicant: Bio Products Laboratory

Product: Immune Globulin Intravenous (Human)
Trade name: Gammaplex®

Subject: Final Review, Original BLA submission, assigned CMC sections

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Recommendation

This original BLA is recommended for approval.

Executive Summary

Specific assigned CMC sections were reviewed and found to be acceptable:

- Stability in the presence of S/D reagents – the -(b)(4)--S/D mixture from the S/D viral inactivation step was stable for ---(b)(4)--- as determined by --(b)(4)--.
- Concentration by ----(b)(4)---- – the -(b)(4)- step done -(b)(4)- S/D incubation to concentrate IgG from --(b)(4)-- was successfully validated, as assessed by ----------(b)(4)----------
- Excipients & Impurities – assay methods for detection of these components in final product were described and validation results were provided; all were acceptable.
- Batch analysis – manufacturing and final-product consistency was demonstrated for -(b)(4)- batches of Gammaplex.
- Characterisation of Impurities – in two conformance lots, levels of processing residuals and non-IgG protein were below assay limits of detection, except for ----------(b)(4)----------
- Justification of final product specifications – BPL bases its final-product release specifications on the ----------(b)(4)---------- requirements for IGIV and on -(b)(4)- years' manufacturing experience; the proposed specifications are acceptable.

- Stability – the provided stability-study data support the proposed storage conditions for final-product Gammaplex of 24 months at 2 °C to 25 °C.

Background Summary

The British biopharmaceuticals firm Bio Products Laboratory (BPL) has submitted a new BLA to apply for U.S.-licensure of a 5% Immune Globulin Intravenous (Human) product, trade name Gammaplex®. This IGIV product is based on the pre-existing BPL IGIV product Vigam Liquid, and is manufactured via ------(b)(4)---------- fractionation to the ----------(b)(4)----------, followed by solvent/detergent incubation, -----(b)(4)------ ion-exchange chromatography, viral filtration, -----(b)(4)----, final formulation to bulk drug substance, sterile filtration, final-product filling, and ----------(b)(4)----------. The starting plasma pool is ----(b)(4)----- and may be subjected to ----------(b)(4)----------.

The final formulation is: --(b)(4)-- protein consisting of ≥95% gammaglobulin, --(b)(4)-- mM sodium chloride, --(b)(4)-- mM glycine, -(b)(4)- mM sorbitol, -(b)(4)- µg/mL polysorbate 80, pH 4.8 – -(b)(4)-, in presentations of 2.5 g, 5 g, and 10 g (i.e., 50, 100, and 200 mL).

Assigned sections include the following:

- Section 3.2.P.3.5.8 (Vol. 5 p. 1564) Stability in the presence of S/D reagents
- Section 3.2.P.3.5.14 (Vol. 5 p. 1572) Concentration by ---(b)(4)---
- Section 3.2.P.5.2.5 (Vol. 5 p. 1729) Excipients (methods)
- Section 3.2.P.5.2.6 (Vol. 5 p. 1735) Impurities (methods)
- Section 3.2.P.5.3.5 (Vol. 6 p. 1790) Excipients
- Section 3.2.P.5.3.6 (Vol. 6 p. 1807) Impurities (validation of methods, etc.)
- Section 3.2.P.5.4 (Vol. 6 p. 1823) Batch analysis
- Section 3.2.P.5.5 (Vol. 6 p. 1844) Characterisation of Impurities
- Section 3.2.P.5.6 (Vol. 6 p. 1851) Justification of specifications for appearance, pH, etc
- Section 3.2.P.8 (Vol. 6 p. 1866) Stability

These sections are reviewed in order, below, except that methods and validations for the test methods for excipients and impurities are reviewed together:

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

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

Appendix 1. --(b)(4)-- plots of submitted stability data: final product

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

One Page Determined to be Non-Releasable: (b)(4)

Appendix 2. Final-container drug product release specifications

	Test	Limits			Compliance Reference
		2.5 g	5.0 g	10 g	
Characteristics	Appearance of solution	Complies			-(b)(4)-
	pH at 20°C	4.8 – -(b)(4)-			-(b)(4)-
	Osmolality, mOsmol/kg	-(b)(4)-			-(b)(4)-
Biological Safety Tests	Sterility	Pass			-(b)(4)-
	Pyrogenicity Δ°C in rabbits	Pass			-(b)(4)-
	Endotoxin (-(b)(4)-), EU/mL	-(b)(4)-			-(b)(4)-
	General Safety Test	Pass			21 CFR 610.11
Viral Marker Tests	Hepatitis Bs Antigen	-(b)(4)-			-(b)(4)-
	Anti-HIV (1 and 2)	-(b)(4)-			-(b)(4)-
Purity/Specific Function	Anti-HBsAg, IU g/IgG	-(b)(4)-			-(b)(4)-
	Anti-HAV, IU g/IgG	-(b)(4)-			-(b)(4)-
	Anti-Parvovirus B19, IU/mg IgG	-(b)(4)-			-(b)(4)-
	-------(b)(4)--------- ----------	-(b)(4)-			-(b)(4)-
	Total protein, g/L	-(b)(4)-			-(b)(4)-
	Protein Composition, gammaglobulin, %	≥ 95			-(b)(4)-
	----------(b)(4)---------- ----------	-(b)(4)-			-(b)(4)-
	Anti-diphtheria	-(b)(4)-			-(b)(4)-/21 CFR 640.104
	Anti-measles	-(b)(4)-			21 CFR 640.104
	Anti-poliovirus	-(b)(4)-			21 CFR 640.104
Excipients	Sodium, mM	-(b)(4)-			-(b)(4)-
	Chloride, mM	-(b)(4)-			-(b)(4)-
	Glycine, mM	-(b)(4)-			-(b)(4)-
	Acetate, mM	-(b)(4)-			-(b)(4)-
	Sorbitol, g/L	-(b)(4)-			-(b)(4)-
	Polysorbate 80, µg/mL	-(b)(4)-			-(b)(4)-
Contaminants	Anti-A, Anti-B Haem-agglutinins -----(b)(4)-----	-(b)(4)-			-(b)(4)-
	Anti-D	-(b)(4)-			-(b)(4)-
	IgA, ------(b)(4)-------	-(b)(4)-			-(b)(4)-
	----(b)(4)----	-(b)(4)-			-(b)(4)-
	---------(b)(4)-------- ----------	-(b)(4)-			-(b)(4)-
	--------(b)(4)--------	-(b)(4)-			-(b)(4)-

Appendix 3. Stability of manufacturing intermediates

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