Summary Basis for Regulatory Action Template

Date: February 02, 2017

From: Yeowon A. Kim, M.D., M.H.S., Clinical Reviewer

BLA/STN#: 125329/151

Applicant Name: Bio Products Laboratory

Date of Submission: April 08, 2016

Goal Date: February 06, 2017

Proprietary Name/ Established Name: Gammaplex 10%/Immune Globulin Intravenous (Human), 10% Liquid

Indication: Primary Humoral Immunodeficiency (in adults), Idiopathic Thrombocytopenic Purpura (in adults)

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority:
Wilson W. Bryan, M.D., Director
Office of Tissues and Advanced Therapies

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Victor C. Baum, M.D. and Yeowon A. Kim M.D., 12/28/2016 Scott K. Winiecki, M.D., 07/08/2016 Erin McDowell, 09/22/2016; Erin McDowell, 01/17/2017
Statistical Review(s)	Shuya (Joshua) Lu, Ph.D., 01/10/2017
CMC Review(s)	Simleen Kaur, 10/05/2016

• *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Malgorzata G. Norton, 09/19/2016 Malgorzata G. Norton, 01/26/2017
Pharmacology/Toxicology Review(s)	N/A
Clinical Pharmacology Review(s)	Iftekhar Mahmood, Ph.D., 09/27/2016
Labeling Review(s) • *APLB (OCBQ/APLB)*	Alpita Popat, PharmD, MBA; 12/22/2016
Advisory Committee Transcript	N/A
Other (list)	Proposed package insert

1. Introduction

This Efficacy Supplement was submitted by Bio Products Laboratory on April 08, 2016, in support of the licensure of Gammaplex® 10%, Immune Globulin Intravenous (Human), 10% Liquid (hereafter Gammaplex 10%) for the indications of primary humoral immunodeficiency (PI) and idiopathic thrombocytopenic purpura (ITP). Gammaplex 10% differs from the licensed product Gammaplex 5% in two major ways: a higher concentration and use of glycine as an excipient instead of sorbitol.

Gammaplex 5% was licensed in the U.S. in 2009 for the treatment of PI in adults, 2013 for ITP in adults, and in 2015 for PI in children two years of age or older. Gammaplex 10% is not yet licensed in any jurisdiction.

On October 24, 2012 (CRMTS 8602), the FDA advised the applicant that a pharmacokinetic bridging or crossover study demonstrating bioequivalent area under the curve (AUC) for Gammaplex 5% and Gammaplex 10% in subjects with PI would be acceptable to license Gammaplex 10% for PI and ITP. This was predicated upon the bioequivalence criterion being met as well as the approval of Gammaplex 5% for ITP. The bioequivalence study, "A Phase III, Multicenter, Open-label, Randomized, Two-Period, Crossover Bioequivalence Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Gammaplex® 10 and Gammaplex® 5% in Primary Immunodeficiency Diseases" is the subject of this submission.

The clinical trial met its primary objective of demonstrating the bioequivalence of Gammaplex 10% and Gammaplex 5% with respect to AUC within a 28-day dosing interval (AUC_{0-28}) in a cohort of adult subjects. In addition, the secondary objective of demonstrating the bioequivalence of Gammaplex 10% and Gammaplex 5% with a 21-day dosing interval was also met, with the exception of adjusted AUC_{0-21} being 1.26 (just outside the upper prescribed bound of 1.25). The trial also met the safety endpoint recommended by the FDA Guidance on studies to support the marketing of IGIV products; the upper one-sided 95% confidence interval for the proportion of infusions with one or more temporally associated AEs (regardless of product relatedness) should be < 0.40.[1] The upper bounds for Gammaplex 10% and Gammaplex 5% in

[1] Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. U.S. Department of Health and Human Services, Food and Drug Administration, CBER, June 2008, p4.

adult subjects were 28.3% and 35.9%, respectively. The safety profiles were comparable between the two formulations and there were no deaths, serious unexpected suspected adverse reactions (SUSARs), thromboembolic events, or hemolytic events in the study.

The revised proposed label is acceptable, and approval of the efficacy supplement is recommended.

2. Background

Gammaplex 5% was licensed in the US in 2009 for the treatment of PI in adults, ITP in adults in 2013, and PI in children two years of age or older in 2015.

PI represents a heterogeneous group of disorders resulting from largely inherited defects of the immune system. Many of these disorders are marked by hypogammaglobulinemia which can increase susceptibility to infections. Replacement therapy with immunoglobulins, either administered intravenously or subcutaneously, is a mainstay of treatment. ITP is an acquired form of thrombocytopenia that is thought to be caused by autoantibodies against platelet antigens. IGIV, glucocorticoids, and anti-RhD immune globulin are first-line therapies for ITP. The mechanism of IGIV in ITP is unknown; however, IGIV is hypothesized to exert immunomodulatory effects via interactions of its Fc fragments with distinct Fcγ receptors.[2,3] The typical IGIV dose used to treat ITP is higher than that used for PI: 1 g/kg for 2 consecutive days vs. 300-800 mg/kg every 3-4 weeks.

Gammaplex 10% is not yet licensed in any jurisdiction although other 10% IGIV products are available from various manufacturers with acceptable safety profiles. IGIV as a drug class carries an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. In March 2013, the Gammaplex 5% label was updated to indicate that it is contraindicated in patients with hereditary fructose intolerance or in infants or neonates for whom sucrose tolerance has not been established. This issue is irrelevant for Gammaplex 10% as glycine replaces sorbitol as an excipient (sorbitol is metabolized to fructose). Glycine-stabilized 10% IGIV products marketed in the US include Gammagard Liquid, Bivigam, Gammagard S/D (freeze-dried preparation that is reconstituted to 5% or 10% solution), and Gamunex-C/Gammaked.

3. Clinical/Statistical/Pharmacovigilance

a) Clinical Program

"A Phase III, Multicenter, Open-label, Randomized, Two-Period, Crossover Bioequivalence Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Gammaplex® 10 and Gammaplex® 5% in Primary Immunodeficiency Diseases" evaluated the PK, safety, and tolerability of Gammaplex 10% and Gammaplex 5% in adults with PI. (b) (4)

[2] Kaneko Y, Nimmerjahn F, and Ravetch JV. Anti-inflammatory activity of immunoglobulin H resulting from Fc sialylation. Science 2006; 313:670-3.
[3] Anthony R, Nimmerjahn F, Ashline DJ, et al. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. Science 2008; 320: 373-6.

(b) (4)

33 adults enrolled and were to receive a total of 10 infusions (5 infusions each of Gammaplex 10% and Gammaplex 5%) at a dose of 300 to 800 mg/kg/infusion. Subjects were randomly assigned to 1 of 2 treatment sequences (5 infusions of Gammaplex 10% followed by 5 infusions of Gammaplex 5% and vice-versa), and infusions were administered on either a 21- or 28-day treatment schedule depending on the subject's prior IGIV regimen. All 33 adults were included in the overall intent-to-treat (ITT) population. Thirty-three adult subjects were included in the ITT population for Gammaplex 5% and 32 were included in the ITT population for Gammaplex 10%. Thirty adults were included in the PK bioequivalence analysis: 2 subjects had incomplete profiles and 1 subject withdrew during the first infusion. A sample size of 16 subjects was deemed adequate for meeting the primary objective with 90% power.[4] No imputation was to be made for missing data.

Subjects were predominantly female (21 subjects, 63.6%). The age range was 17 to 55 years, with a median of 42 years. All subjects were Caucasian. Individual subject doses ranged from 258 to 791 mg/kg for Gammaplex 10% and 169 to 785 mg/kg for Gammaplex 5%. The median dose per infusion was similar for both products: 474 mg/kg for Gammaplex 10% and 476 mg/kg for Gammaplex 5%. The mean total dose was 202 g for Gammaplex 10% and 190 g for Gammaplex 5%. The mean total doses were similar between the 21- and 28-day infusion schedules for both products: 200 g and 204 g, respectively, for Gammaplex 10% and 192 g and 188 g for Gammaplex 5%. Subjects received a total of 166 infusions of Gammaplex 10% and 163 infusions of Gammaplex 5%. The maximum infusion rate allowed during the clinical study was 0.08 mL/kg/min (8 mg/kg/min).

The primary objective of the study was to demonstrate the bioequivalence of Gammaplex 10% and Gammaplex 5% with respect to AUC_{0-28} in adult subjects. Secondary objectives were 1) to demonstrate bioequivalence of Gammaplex 10% and Gammaplex 5% with respect to AUC_{0-21} and 2) to assess the pharmacokinetics (PK) of Gammaplex 10% and Gammaplex 5% and safety and tolerability. The primary safety and tolerability endpoint was measured by number and percentage of adverse events (AEs), including the number and percentage of infusion-related AEs (defined as all AEs that occurred from the start of infusion until 72 hours from the end of infusion).

The clinical trial met its primary objective of demonstrating the bioequivalence of Gammaplex 10% and Gammaplex 5% with respect to AUC_{0-28} in a cohort of adult subjects. In addition, the secondary objective of demonstrating the bioequivalence of Gammaplex 10% and Gammaplex 5% with a 21-day dosing interval was also met, with the exception of adjusted AUC_{0-21} being 1.26 (just outside the upper prescribed bound of 1.25).

The trial also met the safety endpoint recommended by the FDA Guidance on studies to support the marketing of IGIV products; the upper one-sided 95% confidence interval for the proportion of infusions with one or more temporally associated AEs (regardless of product relatedness) should be < 0.40. The upper bounds for Gammaplex 10% and Gammaplex 5% in adult subjects were 28.3% and 35.9%, respectively. The safety profiles were comparable between the two formulations and there were no deaths, serious unexpected suspected adverse reactions

[4] Interim Statistical Analysis Plan, Clinical Study Report, Study GMX-07, Section 7.3, Nov 2015, p 17.

(SUSARs), thromboembolic events, or hemolytic events in the study. Given the safety profile of Gammaplex 10%, it was agreed that routine pharmacovigilance is appropriate as proposed by the applicant.

The Division of Inspections and Surveillance conducted Biomedical Monitoring (BIMO) inspections of two clinical sites, representing 23% of total subjects enrolled in the study. The inspections also focused on specific questions concerning the study protocol and data integrity. The BIMO inspections did not find any deviations from the applicable regulations at either site and both inspections were classified as No Action Indicated (NAI).

b) Pediatrics

This Efficacy Supplement was submitted in support for the licensure of Gammaplex 10% for the treatment of PI and ITP in adults. (b) (4) During a meeting on July 09, 2014, the Pediatric Review Committee (PeRC) concluded that the change in concentration of Gammaplex 10% from Gammaplex 5% does not trigger the Pediatric Research Equity Act (PREA).

c) Other Special Populations

Pregnancy: There are no data with Gammaplex 10%. Animal reproduction studies have not been conducted with the product. Immunoglobulins can cross the placenta increasingly after 30 weeks of gestation. The final label states that Gammaplex 10% should be given to pregnant women only if clearly needed.

Lactation: There are no data with Gammaplex 10%. The final label states that the product has not been evaluated in breast-feeding mothers.

Geriatric Use: No subjects over the age of 55 were included in the study of Gammaplex 10%. This was in accordance with the FDA's preference to limit the adult age range to 19 to 55 years in order to minimize PK variability. The final label states to use caution when administering Gammaplex 10% to patients age 65 and over who are judged to be at increased risk of developing renal insufficiency or thrombotic events, to not exceed recommended doses, and to administer at the minimum infusion rate practicable.

4. Chemistry Manufacturing and Controls (CMC)

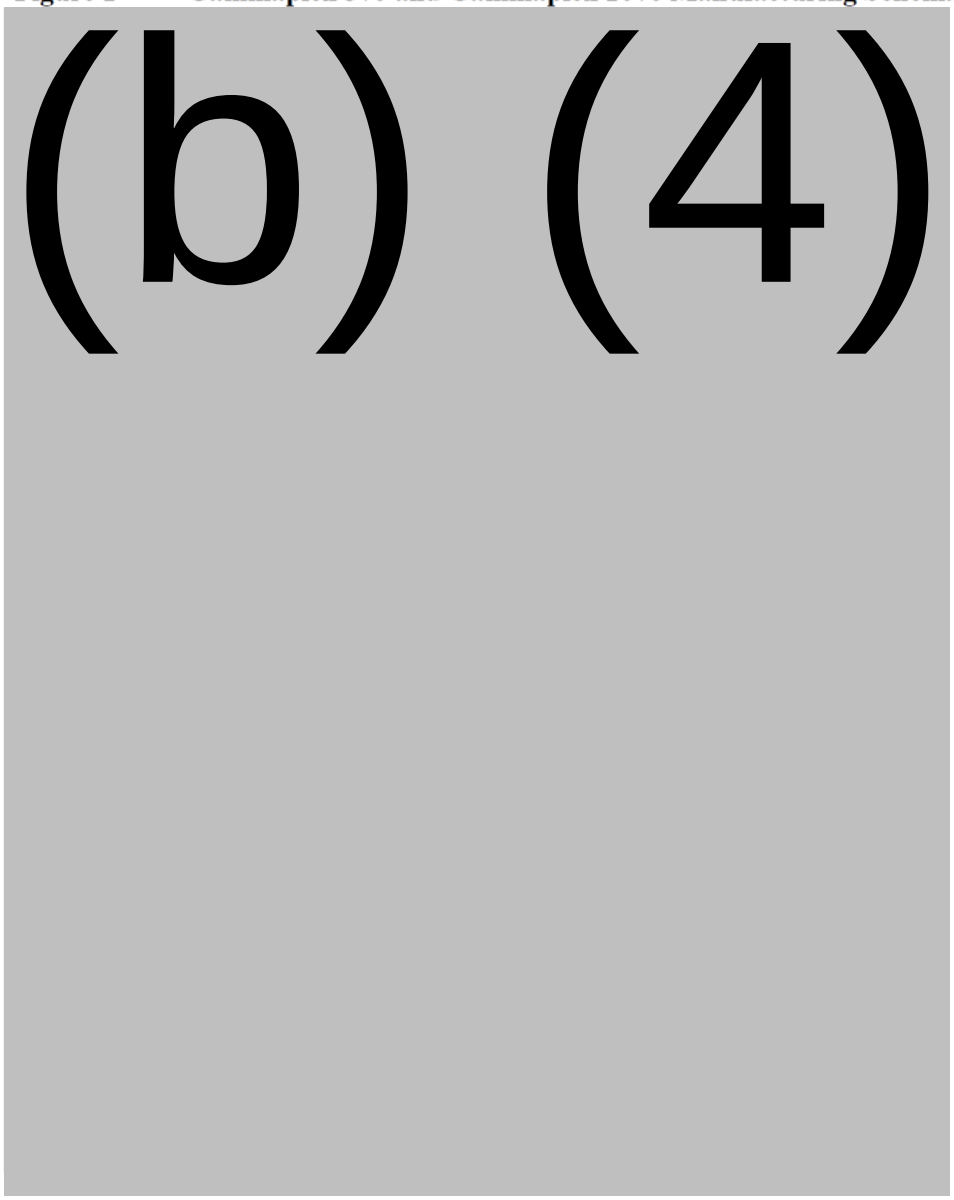
a) Product Quality

Bio Products Laboratory (BPL) Immune Globulin Intravenous (Human), Gammaplex® 10% is a solution of human normal immunoglobulin G (IgG) from healthy U.S. plasma donors. This IGIV product is a modification of the BPL's current IGIV product Gammaplex 5% which is licensed in the U.S. since 2009. Gammaplex 10% differs from Gammaplex 5% by (b) (4) step, and changes in its formulation. Unlike Gammaplex 5%, Gammaplex 10% does not contain sorbitol in its formulation. Instead, the glycine content is raised to 200-300 mM and the polysorbate 80 remains the same at 10-60 µg/mL. Gammaplex 10% is manufactured using (b) (4) fractionation to the (b) (4), followed by solvent/detergent incubation, (b) (4) ion-exchange chromatography, 20 nm nanofiltration, (b) (4), final formulation to bulk drug substance, sterile filtration, final-product filling, with a terminal high temperature/low pH hold (b) (4) product ((b) (4) . BPL performed formulation studies during the development of Gammaplex 10% and the stability studies necessary to support the choices made for the Gammaplex 10% formulation. The final formulation is: (b) (4) protein consisting of ≥ 98% IgG, (b) (4) sodium chloride, 200 - 300 mM glycine, 10 – 60 µg/mL polysorbate 80, pH 4.9 – 5.2. Gammaplex is filled at 50 mL, 100 mL, and 200 mL sizes (5 g, 10 g, and 20 g) in Type II glass bottles.

Source Plasma: As for Gammaplex 5%, BPL obtains U.S. source plasma from licensed plasma centers. The plasma is screened and tested for antibodies to HCV and HIV, including HBsAg, followed by minipool testing by NAT/(b) (4) for HIV, HBV, HCV, HAV and Parvovirus B19. Plasma supplied to BPL is (b) (4), under appropriately validated processes. Prior to fractionation, source plasma is stored at BPL for (b) (4) . Manufacturing plasma pools are tested for anti-HIV1 and anti-HIV2 antibodies, HBsAg, HCV (b) (4) and parvovirus B19 DNA. The parvovirus B19 DNA limit for the manufacturing plasma pools is set as $\leq 10^4$ IU/mL. All other raw materials used in the manufacture of Gammaplex are obtained from appropriately qualified vendors, quarantined on receipt, tested by validated methods, and released to manufacturing by QA personnel.

Manufacturing Process: Gammaplex 10% is a liquid formulation of 100 g/L human IgG, prepared from US source plasma, and is manufactured using a (b) (4) fractionation method. The manufacturing process for the 10% product is (b) (4) to the approved 5% product up to the (b) (4) There are three virus inactivation steps: solvent/detergent, nanofiltration, and low pH incubation at (b) (4) . The final product is formulated with 10-60 µg/mL polysorbate 80 (PS80) and 200-300 mM glycine.

Figure 1 Gammaplex 5% and Gammaplex 10% Manufacturing Schematic



Specifications: Specifications and validation of analytical methods have been evaluated by review personnel. The final specifications and acceptance limits established for Gammaplex 10% by BPL are within the ranges seen for other 10% IGIV products and were determined to be acceptable. The specifications are established based on the results of conformance batches and historical product data from BPL's Gammaplex 5% product. The testing program for Gammaplex includes appropriate measures of product quality attributes, product impurities, and parameters known to effect IGIV safety. All routine methods used as control or release testing of starting materials, process intermediates, drug product, and stability samples, were validated and appropriate implemented. Through discussions with BPL, the (b) (4) assay was added to the lot release testing with a specification of (b) (4) and the (b) (4) , also listed as (b) (4) assay, was set as "for information only" at (b) (4) ; however, since this limit is still above the manufacturing capabilities, BPL was asked to commit to re-validate the (b) (4) and re-assess the

specifications for both assays after (b) (4) in a Post Marketing Commitment. BPL agreed to this commitment on January 25, 2017.

Table 1. Gammaplex 10% Drug Product Specifications

	Test	**Release Limits**	**End of Shelf-life Limits**	**Compliance Reference**
Characteristics	Appearance of Solution	Complies[1]	Complies[1]	(b) (4)
	pH at +20°C	4.9 to 5.2	(b) (4)	BPL (b) (4)
	Osmolality, mOsmol/kg	240 (b) (4)		(b) (4)/FDA/BPL
Biological Safety Tests	Sterility	Pass	Pass	(b) (4)
	Endotoxin ((b) (4)	(b) (4)	(b) (4)	(b) (4)/BPL
Purity/Specific Function	Anti-HBsAg, IU/g IgG	(b) (4)	(b) (4)	BPL (b) (4)
	Anti-HAV, IU/g IgG	(b) (4)	(b) (4)	BPL
	Antibody to Parvovirus B19, IU/mg IgG	(b) (4)	(b) (4)	BPL
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Total Protein, g/L	(b) (4)		(b) (4)
	Protein Composition Gammaglobulin, %	NLT 98		BPL (b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		(b) (4)	(b) (4)	(b) (4).
		(b) (4)	(b) (4)	(b) (4)
	Anti-Diphtheria, antitoxin units/mL	(b) (4)	(b) (4)	21 CFR 640.104
	Anti-Measles	(b) (4) CBER ref lot 176	(b) (4) CBER ref lot 176	21 CFR 640.104
	Anti-Poliovirus	(b) (4) CBER ref lot 176	(b) (4) CBER ref lot 176	21 CFR 640.104
Excipients	Sodium, mmol/L	(b) (4)		BPL
	Chloride, mmol/L	(b) (4)		BPL
	Glycine, mmol/L	200 - 300		BPL

	Test	Release Limits	End of Shelf-life Limits	Compliance Reference
	Acetate, mmol/L	(b) (4)		BPL
	Polysorbate 80, µg/mL	10 to 60		BPL
Impurities	Anti-A, Anti-B Hemagglutinins (b) (4)	(b) (4)		(b) (4)
	Anti-D	(b) (4)		BPL
	IgA, (b) (4)	(b) (4)		BPL
	(b) (4)	(b) (4)		(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)		(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)

[1]Colorless, clear or slightly opalescent and free from visible particles
[2]For information only, not a Release test

Table 2 Gammaplex 10% Labeled Product Specifications

	Test	Limits	Compliance Reference
Purity/Specific Function	Total Protein, g/L	(b) (4)	(b) (4)
	Protein Composition Gammaglobulin, %	NLT 98	(b) (4)

Stability of Final Drug Product: The stability-study data provided in the efficacy supplement was sufficient to support the proposed storage conditions for final-product Gammaplex of 36 months at 2°C to 25°C. Please see the End of Shelf-life Specifications in Table 1 above.

Control of Adventitious Agents: Gammaplex is manufactured only from U.S. source plasma. The plasma is screened and tested for antibodies to HCV and HIV, including HBsAg, followed by minipool testing by NAT/ for HIV, HBV, HCV, HAV and Parvovirus B19. The Gammaplex process contains three manufacturing steps which contribute to viral inactivation or removal - solvent/detergent virus inactivation, 20nm filtration step, and a terminal incubation at high temperature/low pH. These steps are robust and validated to yield the following levels of viral inactivation or removal:

Viral Reduction by Process Step

Virus	Type (Envelope/ Genome)	Size (nm)	Process Log_{10} Reduction of Virus (LRV) over manufacturing step			
			Solvent Detergent	20 nm filtration	Terminal low pH/elevated temperature incubation	Total LRV
HIV	Env/RNA	80-100	>6.8	I	6.0	>12.8
SIN	Env/RNA	70	>6.7	6.2	>5.4	>18.3
WNV	Env/RNA	50	>6.4	I	NT	>6.4
BVDV	Env/RNA	40-60	>5.6	I	>4.0	>9.6
IBR	Env/DNA	200	>5.0	I	>5.4	>10.4
HAV	Non-Env/RNA	30	NA	>4.8	1.5	>6.3
EMC	Non-Env/RNA	30	NA	>4.8	3.4	>8.2
CPV	Non-Env/RNA	18-24	NA	3.2	1.0	4.2

HIV: Human immunodeficiency virus
SIN: Sindbis virus, model for hepatitis C virus (HCV)
WNV: West Nile Virus
BVDV: Bovine viral diarrhea virus, model for HCV
IBR: Infectious bovine rhinotracheitis, bovine herpesvirus model for enveloped DNAviruses including hepatitis B
HAV: Hepatitis A virus
EMC: Encephalomyocarditis, model for HAV
CPV: Canine parvovirus, model for human parvovirus B19
NA: Not applicable, solvent detergent step is limited to the inactivation of enveloped viruses
I: Inactivation by the product intermediate precluded the accurate estimation of the removal of these viruses by the filtration step
NT: Not tested
B19: Viral clearance of human parvovirus B19 was investigated experimentally at the 20 nm filtration step. The estimated Log reduction Factor obtained was 6.0

Clearance of (b) (4) by the major steps shared by the Gammaplex 10% and 5% purification process was demonstrated in the review of manufacturing steps in the Gammaplex 5% BLA. The manufacturing steps were shown capable of achieving the following log10 reductions: (b) (4) However, reduction factors were assessed by (b) (4) and not by (b) (4) assays, so the results cannot be claimed in the product labeling.

b) CBER Lot Release (only applicable for BLAs)

The product is an IGIV, similar to the licensed IGIV product Gammaplex 5% for which CBER does not perform routine lot release testing. Lot release tests performed by the manufacturer BPL are appropriate to assure the safety and potency of this product.

c) Facilities review/inspection

There was no inspection related to this Efficacy Supplement as there were no changes to the facility or equipment. Team Biologics conducted a Level II inspection of Bio Products Laboratory Ltd., Dagger Lane, Elstree, Hertforshire, United Kingdom, FEI 1000184635, during the dates of May 14 – May 22, 2015. Coverage was given to the Quality System and the Facilities and Equipment System, with limited coverage to the remaining systems. The inspection resulted in the issuance of a Form FDA 483, Inspectional Observations, containing 9 observations. The inspection was classified as Voluntary Action Indicated (VAI). It appears that the inspectional issues have been resolved; however, (b) (5), (b) (7)(E) .

d) Environmental Assessment

The BPL facility was recommended for a categorical exclusion under 21 CFR 25.31 (c) on August 21, 2009. Since this is not a new product and there are no changes to the facility, a new Environmental Assessment is not necessary.

e) Product Comparability

The difference between the 5% and 10% formulation is that the 10% does not include Sorbitol, has less Sodium (b) (4)) and Chloride (b) (4) contains a higher concentration of Glycine (200-300 mM) as the primary stabilizer, and has a slightly higher pH (4.9-5.2). The final test results of 10% product are comparable to the already approved 5% product, except for those affected by concentration. The 10% product also has (b) (4) content at the end of shelf-life than the 5% product, which is consistent with some 10% products. Additional in house testing using (b) (4) , also comparable with other 10% IGIVs. The three conformance lots tested are comparable to each other and to the clinical lots submitted under the Gammaplex 10% IND.

Table 3 Differences in Gammaplex 5% and Gammaplex 10% formulations

Composition	**Gammaplex 5% IGIV**[a]	**Gammaplex 10% IGIV**
	Sorbitol Formulation[b]	Glycine Formulation[c]
Active ingredients		
Human IgG (manufactured by Gammaplex process)	50 g/L	100 g/L
Inactive ingredients		
Sorbitol	50 g/L	N/A
Sodium	(b) (4)	(b) (4)
Chloride	(b) (4)	(b) (4)
Glycine	(b) (4)	200-300 mM
Acetate	(b) (4)	< 30 mM
Polysorbate 80	(b) (4)	10-60 µg/mL

Composition	Gammaplex 5% IGIV[a]	Gammaplex 10% IGIV
pH	4.8-5.1	4.9-5.2

[a]Licensed formulation (BL No. 1811)
[b]Sorbitol used as stabilizer
[c]Glycine used as stabilizer

5. Nonclinical Pharmacology/Toxicology

There were no new pharmacology/toxicology data submitted in this efficacy supplement.

6. Clinical Pharmacology

This was a phase III, multicenter, open-label study of Gammaplex 10% and Gammaplex 5% (licensed product) to demonstrate bioequivalence between Gammaplex 10% and Gammaplex 5% in adults with primary immunodeficiency diseases (PID).

Adult subjects received a total of 10 infusions (5 infusions of Gammaplex 10% and 5 infusions of Gammaplex 5%) at a dose of 300 to 800 mg/kg/infusion. Infusions were administered on either a 28-day or 21-day treatment schedule, depending on the subject's cycle of infusions during prior IGIV treatment.

There were 14 subjects on 21-day schedule (2 males and 12 females) and 19 subjects on 28-day schedule (10 males and 9 females). Thirty adults were included in the PK bioequivalence analysis: 2 subjects had incomplete profiles and 1 subject withdrew during the first infusion. Blood samples were collected for the assessment of pharmacokinetics of IgG 30 minutes before infusion, and at 1, 3, 6, 24, 48 hours, and Days 4, 7, 14, 21 (for those who were on 21-day schedule), and 28 following drug administration.

Pharmacokinetic parameters were estimated for each subject by non-compartmental analysis. For bioequivalence analysis, $AUC_{(0-28)}$ and $AUC_{(0-21)}$ of total IgG following the PK infusion were used. The $AUC_{(0-28)}$ and $AUC_{(0-21)}$ data were log-transformed prior to analysis. Each was analyzed using an analysis of variance model from which a 90% confidence interval (CI) for the ratio between formulations was obtained, and which had to lie between 0.8 and 1.25 to demonstrate bioequivalence. The PK and statistical analysis were based on serum concentrations of IgG adjusted for pre-dose concentrations and on absolute (unadjusted) concentrations.

The 90% CIs for the ratios of geometric means (Gammaplex 10%/Gammaplex 5%) for both baseline-adjusted and baseline-unadjusted $AUC_{(0-28)}$ were within the CI of 0.8 to 1.25, indicating that Gammaplex 5% and Gammaplex 10% are pharmacokinetically equivalent in adults. However, the 90% CIs for the ratios of geometric means (Gammaplex 10%/Gammaplex 5%) for

baseline-unadjusted $AUC_{(0-21)}$ were within the CI of 0.8 to 1.25 but not for baseline-adjusted $AUC_{(0-21)}$. The upper limit of CI was 1.26.

CONCLUSIONS: The 90% CIs for the ratios of geometric means (Gammaplex 10%/Gammaplex 5%) for both baseline-adjusted and baseline-unadjusted $AUC_{(0-28)}$ indicate that Gammaplex 5% and Gammaplex 10% are pharmacokinetically equivalent in adults. However, for baseline-adjusted $AUC_{(0-21)}$, the upper limit of CI was 1.26 but not substantially outside the CI interval to declare non-equivalent. Therefore, Gammaplex 10% and Gammaplex 5% are pharmacokinetically equivalent.

7. Safety

There were no deaths, serious unexpected suspected adverse reactions (SUSARs), thromboembolic events, or hemolytic events in the study. No subject had an AE that resulted in discontinuation from the study. No serious adverse events (SAEs) were reported in adult subjects during treatment with Gammaplex 10%. Three SAEs were reported in 2 adult subjects (6.1%) during treatment with Gammaplex 5%. None of the SAEs were considered related to study drug. (b) (4) One was considered to be of moderate intensity and the other was considered to be severe. Both events were considered unrelated to the study drug. Four events of urticaria were assessed as related to study drug

The trial met the safety endpoint recommended by the FDA Guidance on studies to support the marketing of IGIV products; the upper one-sided 95% confidence interval for the proportion of infusions with one or more temporally associated AEs (regardless of product relatedness) should be < 0.40. The upper bounds for Gammaplex 10% and Gammaplex 5% in adult subjects were 28.3% and 35.9%, respectively. There was no evidence of transmission of HBV, HCV, HIV and parvovirus B19. The safety profiles were comparable between the two formulations. The reviewer from the Pharmacovigilance Branch of the Division of Epidemiology recommended that routine pharmacovigilance is appropriate for Gammaplex 10%.

8. Advisory Committee Meeting

There were no issues for the Blood Products Advisory Committee to address.

9. Other Relevant Regulatory Issues

There were no other relevant regulatory issues.

10. Labeling

The final labeling was negotiated and agreed upon. The applicant incorporated FDA's advice to limit the adverse reactions to those that were considered to be causally related to Gammaplex 10%. The viral clearance table was corrected and the "Use in Specific Populations" Section was revised to align with the Physician Labeling Rule. (b) (4)

11.Recommendations and Risk/ Benefit Assessment

The overall risk/benefit ratio is favorable for Gammaplex 10% and the review team recommends approval of this efficacy supplement. Based on the PK data, it is anticipated that Gammaplex 10% has a therapeutic effect similar to Gammaplex 5%. The mean infusion duration is substantially less for Gammaplex 10% than Gammaplex 5%: 111.4 minutes vs. 168.7 minutes in adult subjects. The replacement of sorbitol by glycine permits administration in patients with fructose intolerance.

The safety profiles were comparable between the two products and also to that of IGIV products as a class. Although thrombosis and renal dysfunction/failure have been described with IGIV products, measures to mitigate such events are highlighted in the boxed warning. Given the safety profile of Gammaplex 10%, routine pharmacovigilance is appropriate.

It is noted that the clinical trial was conducted only in PI subjects and did not include those with ITP. Although the safety of Gammaplex 10% has not specifically been established in patients with ITP, the safety profile of Gammaplex 5% has been studied and was found to be acceptable in subjects with ITP. It is anticipated that the safety profile for both formulations are comparable for ITP patients. Hemolysis is a concern with higher doses of IGIV, such as that used for treating ITP, and has been reported in subjects with ITP receiving Gammaplex 5%. Hemolysis is included in both Gammaplex 5% and Gammaplex 10% package inserts in the "Warnings and Precautions" section. Glycine-stabilized 10% IGIV products marketed in the US include Gammagard Liquid, Bivigam, Gammagard S/D (freeze-dried preparation that is reconstituted to 5% or 10% solution), and Gamunex-C/Gammaked. Gammagard S/D and Gamunex-C/Gammaked are approved for ITP. The efficacy and safety profiles of these closely related products in the treatment of ITP support the extension of the proposed Gammaplex 10% indication to include ITP.

On January 25, 2017, the applicant agreed in writing to the postmarking commitment regarding (b) (4) : to re-validate the (b) (4) assay to further (b) (4) and re-evaluate both test specifications after (b) (4) new lots or (b) (4) BPL will submit the (b) (4) assay validation and re-evaluation of the (b) (4) Specifications as a PMC Submission - Final Study Report by September 1, 2019.