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

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To: STN: 125329.0

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Applicant: Bio Products Laboratory (BPL)

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

Subject: Final Review

EXECUTIVE SUMMARY (CMC - Viral Safety)

This submission by BPL for the product of Immune Globulin Intravenous (Human) (Gammaplex) was received by CBER/FDA on Nov 17, 2008 as a BLA. In this submission, the firm provided viral safety data to support the approval of the BLA. These studies include 1) Plasma screening; 2) Analytical assay validation (antibody testing and NAT testing); and 3) Manufacturing procedures that are intended for virus clearance.

All Source Plasma donations are collected in the United States by plasmapheresis. Donor screening for viral markers includes testings for anti-HIV 1 and 2 antibodies, HBsAg, and anti-HCV antibodies. These analytical methods have been validated. Minipools (512 donations/pool) are tested by --(b)(4)-- NAT procedures for HIV, HAV, HBV, HCV and parvovirus B19. Manufacturing plasma pools are tested for anti-HIV1 and 2 antibodies, HBsAg, HCV RNA and parvovirus B19 DNA. The parvovirus B19 DNA limit for the manufacturing plasma pools is set as less than or equal to 10^4 IU/mL.

There are three manufacturing steps that are specifically designed to remove or inactivate viruses; 1) Solvent/detergent treatment; 2) Nanofiltration using Pall Ultipor DV20; and 3) Terminal low pH incubation at elevated temperature ----------(b)(4)----------. Viral validation is performed appropriately at the small-scale that mimics the process of the manufacturing step. In addition, virus reduction by these manufacturing processes is confirmed under worst case conditions.

Information Request was made during the review of the BLA regarding primarily the issues of holding controls of spiked viruses during viral validation at the step of Low pH Incubation. The firm stated that the inactivation of viruses is resulted from the overall effect of low pH (pH -(b)(4)-) and elevated

temperature ----------(b)(4)---------, which consists of the IgG --(b)(4)-- being held at pH --(b)(4)-- (manufacturing limits: 4.8--(b)(4)-) at a temperature of -(b)(4)- (manufacturing limits: -(b)(4)-). The relative contributions of low pH and elevated temperature will be considered in the future study. Thus, the log reduction factor for the low pH incubation step has not recalculated ----------(b)(4)---------- ---------- as indicated in the Information Request by the FDA. As a result, this step has been described to "Terminal low pH/elevated temperature incubation" in the Table 3 of the Package Insert, to illustrate that the figures reflect the total contribution of the low pH incubation, the elevated temperature, and a ----------(b)(4)----------.

Information Request was also made to clarify the limit of the parvovirus B19 DNA in the manufacturing plasma pool and the cut-off level for testing minipools when using -(b)(4)- B19 NAT. The firm confirmed that 1) the limits is set at less than or equal to 10^4 IU/mL 2) the lower limit of quantitation is --(b)(4)--, 3) the assay sensitivity of the B19 NAT (--(b)(4)-- assay -(b)(4)-) is --(b)(4)--.

In addition, *Information Request* was made regarding the sensitivity of HAV NAT for testing manufacturing plasma pools. The firm stated that the 95% detection limit is --(b)(4)-- and that -(b)(4)- HAV --(b)(4)-- assay can detect all genotypes of human origin used in the qualification of the assay.

Finally, *Information Request* was made regarding the claim of Log reduction of parvovirus B19 by nanofiltration. FDA requested that virus titer has to be measured by virus infection assays. -----(b)(4)----- assay is not acceptable for the claim. As a result, the firm agreed to show the estimated viral clearance of B19 by 20 nm filtration as a footnote of the Table 3 in the Package Insert.

Based on the data provided by the firm, efficient removal and inactivation of both the enveloped and non-enveloped viruses by the manufacturing steps are demonstrated (see claimed Log reduction of tested model viruses), thus providing the margin of viral safety of the product.

Summary of claimed Log reduction by manufacturing steps

Virus	**Type (Envelope/Genome)**	**Size (nm)**	**Process Log_{10} Reduction of Virus (LRV) over manufacturing step**			**Total LRV**
			Solvent Detergent	**20 nm filtration**	**Terminal low pH incubation/ elevated temperature**	
HIV	Env/RNA	80-100	>6.8	I	>6.1	>12.9
SIN	Env/RNA	70	>6.7	6.2	>7.3	>20.2
WNV	Env/RNA	50	>6.4	I	NT	>6.4
BVDV	Env/RNA	40-60	>5.6	I	>6.1	>11.7
IBR	Env/DNA	200	>5.0	I	>6.3	>11.3
HAV	Non-Env/RNA	30	NA	>4.8	1.1	>5.9
EMC	Non-Env/RNA	30	NA	>4.8	2.7	>7.5

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
Note: Viral clearance of parvovirus B19 was investigated experimentally at the 20 nm filtration step. The estimated Log Reduction Factor obtained was 6.0.

CMC REVIEW - VIRAL SAFETY

Recommendation

Approval

Overview

This submission by BPL for the product of Immune Globulin Intravenous (Human) (Gammaplex) was received by CBER/FDA on Nov 17, 2008 as a BLA. In the submission, the firm provided viral safety data under this review including 1) Plasma screening; 2) Analytical assay validation (plasma screening tests for antibody and antigen, NAT testing); and 3) Manufacturing procedures that are intended for virus clearance to support the approval of the BLA.

All Source Plasma donations are collected in the United States by plasmapheresis. Minipools (512 donations/pool) are tested by --(b)(4)-- NAT procedures for HIV, HAV, HBV, HCV and parvovirus B19. Manufacturing plasma pools are tested for anti-HIV1 and 2 antibodies, HBsAg, HCV RNA and parvovirus B19 DNA. The parvovirus B19 DNA limit for the manufacturing plasma pools is set as less than or equal to 10^4 IU/mL. Donor screening for viral markers includes testing for anti-HIV-1 and HIV-2 antibodies, HBsAg, and anti-HCV antibodies. These analytical methods have been validated.

Three mechanistically independent manufacturing steps of Gammaplex are validated to claim the removal and/or inactivation of enveloped and non-enveloped viruses; 1) Solvent/detergent treatment; 2) Nanofiltration using Pall Ultipor DV20; and 3) Terminal low pH --(b)(4)-- incubation of the ----(b)(4)----.

Overall, the capacity of the manufacturing process of Gammaplex to remove and/or inactivate both the enveloped and non-enveloped viruses has been validated appropriately. Virus reduction by these manufacturing processes is confirmed under worst case conditions (see claimed Log reduction of tested model viruses), thus providing the margin of viral safety of the product.

Summary of claimed Log reduction by manufacturing steps

Virus	Type (Envelope/Genome)	Size (nm)	Process Log_{10} Reduction of Virus (LRV) over manufacturing step			Total LRV
			Solvent Detergent	20 nm filtration	Terminal low pH incubation at elevated temperature	
HIV	Env/RNA	80-100	>6.8	I	>6.1	>12.9
SIN	Env/RNA	70	>6.7	6.2	>7.3	>20.2
WNV	Env/RNA	50	>6.4	I	NT	>6.4
BVDV	Env/RNA	40-60	>5.6	I	>6.1	>11.7
IBR	Env/DNA	200	>5.0	I	>6.3	>11.3
HAV	Non-Env/RNA	30	NA	>4.8	1.1	>5.9
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NA: Not applicable, solvent detergent step is limited to the inactivation of enveloped viruses
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7 Pages Determined to be Non-Releasable: (b)(4)

Information Request

Requests from FDA on 23 July 2009 have been transcribed in italics for ease of review. Answers from BPL to the IR are presented below.

FDA Request

1. Based on the data provided in this BLA, the log reduction factors (LRF) by the low pH incubation step for all viruses tested including BVDV, HIV, Sindbis, -(b)(4)-*, HAV, IBR, and EMC were calculated by* ----------(b)(4)----------. *Please take the stability of each spiking virus in the hold sample into consideration, and recalculate the LRF accordingly. Please note that if an appropriate comparison is used, LRF for HIV by the low pH treatment should be* -(b)(4)-.

BPL Response

The low pH incubation step models a terminal incubation in the manufacturing process that consists of the IgG --(b)(4)-- being held at pH -(b)(4)- (manufacturing limits: 4.8 - -(b)(4)-) at a temperature of -(b)(4)-- ----------. The inactivation of viruses by this step therefore includes the effect of pH -(b)(4)- and the incubation temperature of -(b)(4)- in combination. In considering the virus reduction contributed by this step we have concentrated on the effect of pH and temperature together. ----------(b)(4)---------- ---------- ---------- ---------- ---------- ----------. Because of the temperature contribution, the most appropriate hold control is a sample of ----------(b)(4)---------- and we expect that there will be minimal inactivation under these conditions (1, 2). The column heading for this step has been changed to 'Terminal low pH/elevated temperature incubation', in Table 3 of the PI, to illustrate that these figures reflect the contribution of low pH and elevated temperature.

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

FDA Request

2. *The addition of* -(b)(4)- *log to the virus reduction of HIV by S/D is inappropriate. Please revise the value for total virus reduction for HIV.*

BPL Response

The figure of -(b)(4)- log has not been added to the virus reduction of HIV by S/D. This figure is the ----------(b)(4)---------- to calculate the LRF.

In Europe, the CHMP guidance states "To make the estimated minimum reduction factor of an effective inactivation process as large as possible, as much processed undiluted materials possible should be sampled"(3). The -(b)(4)- log figure is a result of testing a large volume of sample and is therefore

appropriate. For the HIV S/D a ----------(b)(4)----------. No virus was detected and the virus titre was calculated according to the formula:

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

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

FDA Request
3. Please confirm that the parvovirus B9 DNA limit for your manufacturing plasma pools of Gammaplex is set as less than or equal to10^4 IU/mL.

BPL Response
BPL can confirm that the parvovirus B19 DNA limit for the manufacturing pools of Gammaplex is set at less than or equal to 10^4IU/mL. These data are presented in
3.2.P.5.4 Batch Analysis

FDA Request
4. Please provide the cut-off level for testing minipools of Gammaplex when using -(b)(4)- *Parvovirus B19* ----(b)(4)----- *Assay* -(b)(4)-.

BPL Response
The lower limit of quantitation is ----(b)(4)---, the assay sensitivity of the B19 ----(b)(4)---- Assay -(b)(4)- is --(b)(4)--.

FDA Request
5. *Please provide the assay sensitivity of HAV NAT for testing manufacturing pools of Gammaplex.*

BPL Response
The 95% detection limit is --(b)(4)--.

FDA Request
6. It is stated that -(b)(4)- *HAV* ----(b)(4)---- *assay could detect all 6 HAV genotypes. Please provide data to confirm it.*

BPL Response
-(b)(4)- have confirmed that the HAV ---(b)(4)--- assay can detect all 6 genotypes, and have stated that the data required are contained within their Drug Master Files that are filed with FDA. The reference numbers are:
----------(b)(4)----------

Reviewer's comment: There are 6 genotypes for HAV, 4-6 genotypes are simian, not human origin. However, in --------(b)(4)-------- didn't mention that -(b)(4)- can detect all 6 genotypes. -(b)(4)- compared known isolates in the --(b)(4)--. Despite of mismatches of their primers with probe sequences, -(b)(4)- claims that -(b)(4)- procedure can detect all isolates.

FDA Request
7. Since all plasma donations used in the manufacture of this IGIV product made by BPL were tested by -(b)(4)- *NAT procedures for HIV/HCV/HBV/B19/HAV,* -(b)(4)- *needs to provide us a letter that they allow BPL to cross reference their FDA licensed NAT procedures for HIV-1/HCV, investigational NAT procedures for HBV, and in-process NAT procedures for parvovirus B19 and HAV in Master files.*

BPL Response
The letter authorizing BPL to cross reference their FDA licensed NAT procedure was sent to Debbie Cordaro on 31st July 2009.

FDA Request
8. Please provide the SOPs that describe the management of positive donations/donors for all 5 viruses screened by -(b)(4)- *NAT procedures.*

BPL Response
The SOP entitled BPL0003306SOP Review of Post Donation Information US Plasma is appended to this RFI.

FDA Request
9. Please note that for the claim of log reduction of parvovirus B19 by nanofiltration, virus titer has to be measured by virus infection assays. --------(b)(4)------- *assay is not acceptable for the claim (Please see the acceptable B19 statement provided as footnote to the table in the revised PI).*

BPL Response
The table in the PI has been supplemented with a figure for the reduction of an animal parvovirus by nanofiltration as this is measured using an infectious assay. The B19 data has been added as the suggested footnote.