



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

To: BLA STN 125389\0 File

From: Maria L. Virata-Theimer, Ph.D., LPD/DH/OBRR, HFM-345

Through: Dorothy E. Scott, M.D., Chief, LPD/DH/OBRR, HFM-345

CC: Pratibha Rana, RPM, DBA/OBRR, HFM-380

Applicant: Biotest Pharmaceutical Corporation, Boca Raton, FL

Product: Immune Globulin Intravenous (Human), 10%
Proposed Trade name: Bivigam™

Subject: Final CMC Review: Original BLA - Product Specifications, assigned Analytical Procedures and their Validation Studies, Nucleic Acid Testing of Viruses in Plasma Pools, Transmissible Spongiform Encephalopathy Safety

Executive Summary

This Final Review memorandum covers the review of some assigned CMC sections of the original Biologics License Application (BLA) submission from Biotest Pharmaceutical Corporation (BPC), for Immune Globulin Intravenous (Human)(IGIV), 10% (IGIV) with the proposed trade name, “Bivigam™”, which was received by FDA CBER on 3-NOV-10. The CMC sections reviewed were: Product Specifications, specific Analytical Procedures and their Validation Studies (namely, -----(b)(4)-----
-----, Anti-polio potency, Anti-Measles potency, Anti-Diphtheria potency, -----
(b)(4)-----, Particulate Matter), Nucleic Acid Testing (NAT) of viruses in plasma pools, and Transmissible Spongiform Encephalopathy (TSE) safety. My findings are as follows:

Bivigam is made from Source Plasma at the BPC facility in Boca Raton, FL. Each plasma donation is tested using FDA-licensed serological assays for hepatitis B virus surface antigen (HBsAg) and antibodies to human immunodeficiency virus types 1 and 2 (HIV-1/-2) and hepatitis C virus (HCV). Minipool NAT testing of Source Plasma for HIV-1, hepatitis B virus (HBV), HCV, Parvovirus B19 (B19), and hepatitis A virus (HAV) is also performed through BPC’s plasma suppliers as part of the release testing. Only negative/non-implicated plasma units are shipped to BPC. Manufacturing pools samples are tested by NAT as -----(b)(4)----- for -----(b)(4)----- B19, -(b)(4)-. The limit for B19 DNA in the manufacturing pool is set not to exceed 10⁴ IU/mL.

The final product specifications and acceptance limits established for Bivigam were based on the results of conformance and full-scale lots and clinical trial lots; almost all of these limits are within the ranges seen for other licensed 10% IGIV products (except for Polysorbate 80) and are acceptable.

The routine analytical methods I reviewed that are used for the control or release testing of starting materials, drug substance, drug product, and stability samples were adequately validated.

The risk of transmission of variant Creutzfeldt-Jakob Disease (vCJD) from Bivigam was assessed by BPC and found to be extremely low. According to BPC, the Bivigam manufacturing process has several steps that have been demonstrated in published reports to be capable of removing prions. Although BPC did not perform actual studies on TSE removal for Bivigam, Dr. Dorothy Scott and I evaluated their cleaning procedures and found them to be sufficient in removing prions.

For the CMC sections that I reviewed, I found the data and information provided by the sponsor to be sufficient and acceptable to support the licensure of Bivigam. However, one commitment remains to be fulfilled: -----(b)(4)----- This particular issue should not hold up the approval of the BLA and may be included as a Postmarketing Commitment (PMC) item in the approval letter.

Recommendation

Approval, with the following Postmarketing Commitment (PMC):

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

Background Summary

FDA CBER received on 3-NOV-10 this original Biologics License Application (BLA) submission from Biotest Pharmaceutical Corporation (BPC), for Immune Globulin Intravenous (Human)(IGIV), 10% (IGIV) with the proposed trade name, “Bivigam™” (also referred to as Biotest-IGIV). Bivigam’s proposed indication is for the treatment of patients with primary immunodeficiency diseases (PID). At the end of the 10-month review cycle, FDA CBER issued BPC a Complete Response (CR) letter for various deficiencies on 1-SEP-11. BPC resubmitted the BLA to FDA CBER on 26-OCT-11 to address the CR items.

Michael Kennedy, Ph.D. and Lilin Zhong of LPD/DH/OBRR, HFM-345 are the co-chairs of this BLA submission. My CMC review focused on the review of the Product Specifications, assigned Analytical Procedures and their Validation Studies (namely, , -----(b)(4)-----, Anti-polio potency, Anti-Measles potency, Anti-Diphtheria potency, -----(b)(4)-----, Particulate Matter), Nucleic Acid Testing (NAT) of viruses in the plasma pools, and Transmissible Spongiform Encephalopathy (TSE) Safety.

Supplement Review Summary

Bivigam is a sterile 10% protein solution for intravenous administration, containing 5 g IgG/50 mL or 10 g IgG/100 mL formulated in (b)(4) mM glycine, (b)(4) mM NaCl, and (b)(4) polysorbate 80 at pH 4.0-4.6, without any sugar stabilizer, or albumin. Bivigam is manufactured from ---(b)(4)--- of human Source Plasma (----- (b)(4)----- collected from healthy donors) according to a modified Cohn-Oncley cold alcohol fractionation process and with two added viral inactivation steps (solvent/detergent treatment with Triton X-100 and tri-n-butyl phosphate; nanofiltration using a 35 nm filter). The proposed shelf life of Bivigam is 24 months, stored at 2-8 °C.

The bulk drug substance (BDS) is manufactured at the BPC facility in Boca Raton, FL. -----(b)(4)----- then receives the BDS manufactured by BPC. (b)(4) is responsible for receipt and storage of the BDS -----(b)(4)-----, filling (into 50 mL and 100 mL vials), visual inspection, labeling and packaging of the Bivigam final drug product. In addition, (b)(4) is responsible for having sterility test and particulate matter assay performed at -----(b)(4)----- . BPC is then responsible for the final drug product storage and distribution, regulatory release and for performing and overseeing the remaining drug product release tests, including the pyrogen and potency testing at various contract quality control testing laboratories.

I. Product Specifications, Selected Analytical Procedures and their Validation Studies

In-process and lot release testing are performed primarily at the BPC QC Laboratory Services Department in Boca Raton (except for a few specific tests that are performed at contract testing laboratories). In Tables 1 and 2 below, I compared the proposed product specifications of Bivigam (Biotest-IGIV) with those of BPC's licensed hepatitis B immune globulin product, Nabi-HB, a 5% protein solution containing antibodies to hepatitis B surface antigen (from the 2009-2010 Nabi-HB Annual Report, STN 103945/5311, received 23-DEC-10), assuming that the manufacturing process for Bivigam will be similar to that of Nabi-HB. For a few particular product specifications, I also compared Bivigam's specifications with those of other licensed 10% IGIV products (see Reviewer's Comments below). BPC's revisions sent over the course of the BLA review from various information requests (IR) have been incorporated into the Specification tables below.

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

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

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

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

Table 2: Proposed Specifications for Biotest-IGIV Drug Product (unlabeled vials) compared to those of Nabi-HB

SOP No. and Method	Biotest-IGIV (10%)	Nabi-HB (5%)
	Clear to slightly opalescent liquid; colorless to pale yellow; free of turbidity and visible particles	Clear yellow
	4.0-4.6	
	90-110 g/L	
	(b)(4)	(b)(4)
(b)(4)	≥ 96% Gamma Globulin	≥ 96%
	Human - Positive	
	100-140 mM	
(b)(4)	200-290 mM	
	0.15-0.25%	
	(b)(4)	
(b)(4)	(b)(4)	
	(b)(4)	
	(b)(4)	
(b)(4)	Meets 21 CFR 610.12 requirements	Meets
(b)(4)	Meets USP requirements at the 21 CFR 610.13 dose	Meets
(b)(4)	(b)(4)	
	≥ 0.60 x CBER Ref Std Lot 176 or ≥ internal std	
	(b)(4)	(b)(4)
	(b)(4)	
	(b)(4)	

(b)(4)

Table 3: Proposed Specifications for Biotest-IGIV Drug Product (packaged vials) compared to those of Nabi-HB

Test	SOP No. and Method	Biotest-IGIV (10%)	Nabi-HB (5%)
(b)(4) Purity (Protein Composition)	(b)(4)	≥ 96% Gamma Globulin	No information
Identity (Human)	(b)(4)	Human - Positive	No information

Reviewer's Comments:

-----.

14. Heat stability specification: Nabi-HB has a heat stability specification of “No gelation after heating at 57 °C ± 2 °C after 4 hours”. However, BPC did not set specification for heat stability for Bivigam, stating that Bivigam does not meet the requirements for heat stability as described in 21 CFR 640.101(a), i.e., it has a low pH of (b)(4); but when the pH is adjusted to pH (b)(4), Bivigam meets the requirement for heat stability test. They said that they will agree to implement and validate a modified heat stability test if FDA CBER finds this a necessary test for product release. FDA CBER decided not to pursue this issue further, since the heat stability test is required for intramuscular immune globulin products, but not for IGIV products, and that IGIV manufacturers do not typically test for heat stability at lot release (see response to IR question 20 in Amendment 9).

15. -----

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

-----.

16. Date of manufacture: BPC said that the date of manufacture is considered to be the date of final sterile filtration completed ----- (b)(4) ----- (see response to IR question 23 in Amendment 9).

II. Nucleic Acid Testing (NAT) of Viruses in Plasma Pools

In Table 4 below, BPC provided the following information (originally from Table 3.2.S.2.3.1-1, Section 3.2.S.2.3, Control of Materials), which lists the plasma pool specifications and associated tests for testing the presence of viruses and anti-viral antibodies in Source Plasma used in the manufacture of Biotest-IGIV.

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

BPC provided more information on their NAT testing of plasma pools for blood-borne viruses in Amendment 2 (received 23-DEC-10, see their responses to IR questions 2-6). See also my review of the --(b)(4)-- HAV NAT below in Responses to the 5-JAN-11 Information Request (Amendment 3, received 14-JAN-11).

Draft Package Insert Wording on Parvovirus B19 NAT Testing and Manufacturing Pool Limit

In the original BLA’s draft package insert, the second paragraph of Section 11, Description, lacked a statement on the Parvovirus B19 manufacturing pool limit which FDA CBER has recommended to other manufacturers as per the July 2009 FDA Guidance, “Nucleic Acid Testing to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products”. I recommended to BPC that they use B19 wording similar to that in the Nabi-HB package insert:

“NAT for parvovirus B19 (B19) DNA is also performed on pooled samples of all Source Plasma and the limit for B19 DNA in a manufacturing pool is set not to exceed 10⁴ IU/mL. “

BPC agreed to revise their B19 wording to the abovementioned recommended wording (see response to IR question 22, Amendment 9, received 9-MAY-11)

III. TSE Safety of Bivigam

A. Draft Package Insert Wording on TSE

The original BLA’s draft package insert contained the following statements on their product’s risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD):

1) On the first page of the package insert, under Warnings and Precautions:

“This product is made from human plasma and may contain infectious agents (e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent).”

2) On the page 3 of the package insert, under Section 5 Warnings and Precautions, 5.3 Transmissible Infectious Agents:

“A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) or its variant (vCJD) is also considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM.”

In their Adventitious Agents Safety Evaluation report (BE-T:E-005-012-09-BD, dated 05-MAY-10), BPC stated that they believe that the risk of transmitting vCJD from their product is extremely low. The risk of a vCJD-positive donation entering the plasma pool was calculated to be -----(b)(4)----- manufacturing pool with (b)(4) donations of (b)(4) each [based on a formula recommended by ----- --(b)(4)----- because only US plasma will be used to make Bivigam and that there have not been native cases of vCJD in the US. In addition, they said that no animal-derived material and no specified risk material are used during the production process of Bivigam.

BPC also stated that in the same report that the manufacturing process of Bivigam has several steps that have been demonstrated to be capable of removing prions (based on published reports, see Table 5 below):

1. -----(b)(4)-----
2. -----(b)(4)-----
3. -----(b)(4)-----
4. -----(b)(4)-----
5. -----(b)(4)-----
6. -----(b)(4)-----

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

Reviewer Comments: (1) The proposed wording on page 1 of their draft package insert regarding TSE risk complied to some degree with the recommended wording for the warning section of “plasma-derived products other than albumin” stated in the May 2010 FDA Guidance for Industry, “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products”, as the following:

“Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.”

(2) On the other hand, the proposed wording on page 3 of their draft package insert (Section 5: Warnings and Precautions) was revised (see final version of Package Insert).

(3) All the references listed above in Table 5 (or Table 22 of the report), except the one by -(b)(4)-, were also cited in the -----(b)(4)-----.

B. TSE Clearance Studies

BPC confirmed that they have not performed studies on TSE removal for Bivigam and are not planning to do so because of the calculated low risk of transmission (based on their risk assessment results in their Adventitious Agents Safety Evaluation report, BE-T:E-005-012-09-BD).

C. Cleaning Methods in Relation to Prion Removal

In Section 3.2.A.1.3.3, Equipment Cleaning and Sanitization, page 8 of 46) the typical cleaning sequences and cleaning solutions for each cleaning method are as follows:

1. -----
------(b)(4)-----
-----.
2. -----
------(b)(4)-----
-----.
3. -----
------(b)(4)-----
-----.
4. -----
------(b)(4)-----
-----.

Reviewer’s Comments: (1) The pH of the final working solutions of the --(b)(4)-- detergent is pH (b)(4).

(2) A slide presentation was given by Dr Christoph Kempf of the Plasma Protein Therapeutics Association (PPTA) at the July 2003 TSE Advisory Committee meeting which listed the commonly used inactivation solutions for decontaminating plasma product facilities. For NaOH solutions, the ranges were 0.05 to 1.0M, 4-65 °C, 10 minutes to several hours.

(3) After consultation with Dr. Dorothy Scott (email from 10-AUG-11), it was determined that the use of -----(b)(4)----- caustic detergents for -----(b)(4)---- temperature of (b)(4) were sufficient. She said that “the combination of heat, basic solution, time and detergent is very good generally for TSE clearance for -----(b)(4)---- with caustic detergent should also be robust... The cleaning looks adequate and better than some other firms with respect to the temperature for (b)(4).”

(4) The following references provided by Dr. Scott supported the use of -----(b)(4)---- solution in prion control:

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

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

IV. Responses to Information Requests and Complete Response Letter Items

A. Responses to the 10-DEC-10 Information Request (received on 23-DEC-10 in Amendment 2)

The original BLA submission did not contain supporting documents with details on the NAT testing of plasma pools for blood-borne viruses, e.g., Human Immunodeficiency Virus (HIV), Hepatitis A, B, and C Viruses (HAV, HBV, and HCV, respectively), and parvovirus B19 (B19), therefore, an information request was sent to BPC on 10-DEC-10. Responses from the firm that were received on 23-DEC-10 in Amendment 2 are summarized below:

1. Will you be using Source Plasma only for the manufacture of Biotest-IGIV? Or are you planning to use recovered plasma as well and/or in combination with Source Plasma?

BPC confirmed that only Source Plasma (and not recovered plasma) will be used in the manufacture of Biotest-IGIV.

2. What is the current status with regards to screening HIV, HBV, HCV, parvovirus B19 and HAV in terms of minipool and manufacturing pool testing?

BPC confirmed that minipool NAT testing of Source Plasma for HIV, HBV, HCV, B19, and HAV is performed through Biotest's plasma suppliers as part of the release testing. Only negative/non-implicated plasma units are shipped to BPC. Manufacturing pools samples are tested by NAT as -----(b)(4)----- for -----(b)(4)----- B19, --(b)(4)--.

3. Please provide the pool sizes, NAT sensitivities, and cut-off levels for minipool testing and original single plasma donation for each of these viruses.

BPC provided the information listed below in Table 6. The minipool NAT testing of viruses is performed primarily at the -----(b)(4)-----
----- serve as alternative testing laboratories.

Table 6: Minipool NAT Testing of Source Plasma for manufacture of Biotest-IGIV

Test Parameter	Methodology	Pool Sizes (minipool testing)	Minipool Assay Sensitivity (IU/mL)	Single Donation Assay Sensitivity (IU/mL)
HBV	(b)(4)			
HCV				
HIV				
Parvovirus B19				
HAV				

* Action Limit on an individual sample basis.

Reviewer's Note: BPC later decided to drop the -----(b)(4)----- as an alternative NAT testing lab for manufacturing pool testing (see Amendment 19).

Reviewer's Comments: -----

4. Please provide the pool sizes, NAT sensitivities, and cut-off levels for manufacturing pool testing for each of these viruses.

BPC provided the information in the Table 7 below. The manufacturing pool NAT testing of viruses is performed primarily at the -----
---(b)(4)----- serve as alternate/back-up testing laboratories.

Table 7: Manufacturing pool NAT testing of Source Plasma for manufacture of Biotest-IGIV

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

Reviewer's Note: BPC later decided to drop the -----(b)(4)----- as an alternative NAT testing lab for manufacturing pool testing (see Amendment 19).

5. Please confirm that the parvovirus B19 DNA limit for each of your manufacturing pools for the production of Biotest-IGIV is set not to exceed 10⁴ IU/mL.

BPC confirmed that the B19 DNA limit for each manufacturing pool is set not to exceed 10⁴ IU/mL. They revised their Section 3.2.S.2.3, Control of Materials, to specifically state this B19 DNA limit.

6. Please provide a detailed summary about how the quarantine and proper disposal of NAT-positive donations for HIV/HBV/HCV/B19/HAV are done.

The quarantine and disposal of NAT-positive donations for HIV/HBV/HCV/B19/HAV are done at the plasma collection centers per their FDA-approved SOPs for quarantine and disposal of biohazardous waste. BPC's Source Plasma suppliers do not ship NAT-positive units to BPC's off-site storage facility of Storage Distribution Center. They only ship units to BPC after all testing is completed and the units are released for distribution. Units that are NAT-negative located at the Boca Raton facility, but have been associated with a recently collected and tested NAT-positive unit, will be processed using SOP QA2006, "Notification and Disposition of Associated Lookback Units".

Reviewer's Comment: BPC provided SOP QA2006, which includes a Class A event notification for instances when a plasma unit from a donor probable or confirmed of variant Creutzfeld-Jakob Disease (vCJD) is included in the manufacturing pool (aside from required notification within 5 working days, this could also result in a recall).

Reviewer's General Comments: BPC's responses to the IR were adequate and acceptable

B. Responses to the 5-JAN-11 Information Request (received 14-JAN-11 in Amendment 3)

(b)(4)

- (b)(4) -----:
- a. ----- (b)(4) -----
 - b. ----- (b)(4) -----

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

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

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

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

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

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

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

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

C. Responses to the 7-APR-11 Information Request (received 9-MAY-11 in Amendment 9)

The questions I sent were re-numbered as no. 15- 24 in the response package.

15. Please verify which testing laboratories are going to perform the following release tests:

- a. Are the tests for Appearance and Sterility performed solely at Biotest and/or, in addition, at ----- (b)(4) -----?**

BPC said that the sterility testing will be performed by ----- (b)(4) ----- (Section 3.2.P.3.1 of BLA), while appearance testing will be performed at the BPC facility in Boca Raton, FL. BPC also clarified that ----- (b)(4) ----- is the contract manufacturer for Biotest-IGIV, while ----- (b)(4) ----- is not (Section 3.2.P.3.1 of BLA).

- b. Is ----- (b)(4) ----- going to be an alternate/back-up testing laboratory for the ----- (b)(4) ----- purity (protein composition) test?**

BPC said ----- (b)(4) ----- will not be an alternate/back-up testing laboratory for the ----- (b)(4) ----- purity test for Biotest-IGIV.

- c. Is the pyrogenicity test performed solely at ----- (b)(4) ----- or will ----- (b)(4) ----- serve as an alternate/back-up testing laboratory?**

----- (b)(4) ----- will be the only testing laboratory for the pyrogenicity test for Biotest-IGIV.

16. a. Please propose a specification for Total IgA in the Biotest-IGIV (i.e., specify an amount or limit) based on your conformance lot data.

BPC proposed an interim Total IgA specification of $\leq 200 \mu\text{g/mL}$ based on -----
----- (b)(4) -----

- b. Please commit to setting the Total IgA release specification for Biotest-IGIV ----- (b)(4) ----- after manufacturing a minimum of (b)(4) full-scale commercial lots.**

BPC committed to setting the Total IgA release specification for Biotest-IGIV based on a statistical analysis of Phase 1 and 2 conformance lots and a minimum of (b)(4) full scale commercial lots.

Reviewer's Comment: See follow-up to the commitment in Amendment 15 below.

17. Please revise the wording of your specifications for:

- a. ----- (b)(4) -----**

BPC agreed to revise their ----- (b)(4) ----- specification to the proposed wording.

Reviewer's Comments: (1) BPC later set the final ----(b)(4)---- specification as -----(b)(4)----- (see response to IR question 3b in Amendment 15).

(2) 21 CFR § 640.101(a) heat stability test only applies to intramuscular immune globulin products, not IGIV products. IGIV manufacturers do not typically test for heat stability. Based on these, I decided not to pursue the heat stability testing issue further.

- 21. We recommend that you check the May 2010 FDA Guidance for Industry, “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Product”, for the recommended wording for the Warning Section. Please revise your Warning and Precautions sections on pages 1 and 3 accordingly.**

The package insert has been revised to include the following statement in the Section 5.8, Transmissible Agents:

“Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.”

- 22. Please include a statement on parvovirus B19 NAT testing and the B19 DNA manufacturing pool limit in Section 11, Description (second paragraph) of your package insert, e.g., “NAT for parvovirus B19 (B19) DNA is also performed on pooled samples of all Source Plasma and the limit for B19 DNA in a manufacturing pool is set not to exceed 10⁴ IU/mL”.**

The package insert has been revised to include the following statement in the Section 11, Description:

“NAT for parvovirus B19 (B19) DNA is also performed on pooled samples of all Source Plasma and the limit for B19 DNA in a manufacturing pool is set not to exceed 10⁴ IU/mL”.

- 23. What do you consider as the “date of manufacture” for each Bivigam lot?**

The date of manufacture for each Biotest-IGIV drug product lot is considered to be “the date of the final sterile filtration completed -----(b)(4)-----”.

- 24. Your anti-measles antibody specification is currently set at “≥ 0.60 x Ref (176 CBER)”. Please take note that FDA CBER has allowed manufacturers to lower their anti-measles antibody specification from “≥ 0.60 x Ref (176 CBER)” to “≥ 0.48 x Ref (176 CBER)” due to the observed trend of declining anti-measles titers in the US donor population (Audet, S. *et al*, J. Infect. Dis. 2006; 194:781-9) - provided that they submit the change as a Prior Approval Supplement and agree to do the following: a) report measles in a PIDD patient as a 15-day adverse event report; b) labeling changes to address dosage adjustments for patients with actual or potential exposure to measles; and c) a postmarketing commitment to measure trough levels in a patient receiving a known dose of measles antibodies (may be done in the context of a previous, ongoing or planned efficacy trial)(see May 1-2, 2008 Blood Products Advisory Committee presentation: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4355S1-6_files/frame.htm).**

At this time, BPC wishes to have the specification for anti-measles antibody remain as “≥ 0.60 x Ref (176 CBER)”.

Reviewer's General Comments: BPC's responses were adequate and acceptable, however, a few issues had not been resolved yet, specifically: the choice of the anti-Diphtheria potency testing method, the method SOP and validation reports to -----(b)(4)-----, the ---(b)(4)--- specification and test method validation. These issues were included in the CR Letter to the sponsor, dated 1-SEP-11.

In conjunction with this particular IR, BPC stated in Amendment 19 that since -(b)(4)- was unable to confirm that their assay is sensitive enough to detect HAV genotype II, they decided to drop --(b)(4)-- as an alternative NAT testing laboratory for testing of their -----(b)(4)----- . They have updated Sections 2.3.S.2 and 3.2.S.2.1 such that --(b)(4)-- has been removed as a quality control testing laboratory for -----(b)(4)----- testing of both HAV and B19 (see revised tables in Amendment 19).

Reviewer's General Comments: The sponsor's responses to the CR issues I covered are adequate and acceptable, however, one commitment was not fulfilled: the method -----(b)(4)----- . This particular issue should not hold up the approval of the BLA and may be included as a (b)(4) item in the approval letter. The method transfer to the new testing site should probably be submitted as a Prior Approval Supplement.

APPENDIX

A. Supporting Documents in the Original BLA Submission that were reviewed:

1. 2.3.P.6 Reference Standards or Materials (dated 20-NOV-09)
2. 2.3.S.5 Reference Standards or Materials (dated 20-MAY-10)
3. 3.2.S.2.1 Manufacturer(s) (dated 10-MAY-10)
4. 3.2.S.2.3 Control of Materials (dated 12-MAY-10)
5. 3.2.S.3.2 Impurities (dated 10-MAY-10)
6. 2.3.S.4 Control of Drug Substance (dated 20-AUG-10)
7. 2.3.S.5 Reference Standards or Materials (dated 20-MAY-10)
8. 3.2.S.4.1 Specification (of Biotest IGIV-drug substance)(dated 12-MAY-10)
9. 2.3.P.6 Reference Standards or Materials (dated 20-NOV-09)
10. 3.2.A.1 Facilities and Equipment (dated 20-JUL-10)
11. 3.2.P.1 Description and Composition of the Drug Product (dated 20-MAY-10)
12. 3.2.P.5 Control of Drug Product (dated 12-OCT-10)
13. 3.2.P.5.1 Specification (of Biotest IGIV-drug product)(dated 12-MAY-10)
14. 3.2.P.5.2.1 Appearance (dated 3-MAY-10)
SOP QC2130 Visual Evaluation of IgG -----(b)(4)----- Final Fill Products (version 6, approved 18-MAR-10)
15. 3.2.P.5.2.10 -----(b)(4)----- (dated 3-MAY-10)
SOP QC2194 Determination of -----(b)(4)----- in Aqueous Samples (version 7, approved 31-MAR-10)
3.2.P.5.3.10 -----(b)(4)----- (dated 3-MAY-10)
00-V003-98 Determination of -----(b)(4)----- in Formulated Immune Globulins (dated 31-AUG-98 and 9-SEP-98)
VP-FR-0383 Assay Transfer Protocol Final Report for the -----(b)(4)----- Assay (effective 2-MAR-99)
VP-FR-0383-4 Assay Reagent Stability Evaluation for Determination of -----(b)(4)----- in Aqueous Samples (approved 31-MAR-10)
VP-FR-0383-5 Addendum to Method Validation for -----(b)(4)----- in Formulated Immune Globulins (approved 3-FEB-10)
16. 3.2.P.5.2.11 -----(b)(4)----- (dated 3-MAY-10)
3.2.P.5.3.11 -----(b)(4)----- (dated 3-MAY-10)
SOP QC2058 -----(b)(4)----- Assay (revision 10, approved 14-DEC-09)
00-V022-97 Method Validation for -----(b)(4)----- Assay (approved 1-DEC-97)
VP-FR-0422 Assay Transfer Protocol Final Report for the -----(b)(4)----- Assay (effective 22-MAR-00)
VP-FR-00-V022-97-1 Addendum to Method Validation for -----(b)(4)----- Assay (approved 30-NOV-09)
17. 3.2.P.5.2.12 -----(b)(4)----- (dated 19-MAY-10)
SOP LAB3013 Determination of -----(b)(4)----- Activity in Biotest Immune Globulins, Intravenous drug product, Using the -----(b)(4)----- Method (version 1, approved 20-MAY-10)
18. 3.2.P.5.2.15 IGIV Potency (Polio Titer)(dated 3-MAY-10)
SOP V-5355/04-09 -----(b)(4)----- Test for the Detection of Poliovirus Antibodies (effective 02-MAR-09)
3.2.P.5.3.15 IGIV Potency (Polio Titer)(dated 3-MAY-10)
19. 3.2.P.5.2.16 IGIV Potency (Measles Titer)(dated 3-MAY-10)
SOP V-6807/01-10 -----(b)(4)----- Assay for Measles Antibodies – Modified SOP for Testing Immunoglobulins from Biotest Pharmaceuticals Corporation (effective 15-JUN-10)
3.2.P.5.3.16 IGIV Potency (Measles Titer)(dated 28-JUL-10)

3. VP-IR-3472 Interim Report of Validation for Determining Purity and Identity of -----(b)(4)-----
----- (approved 27-APR-10)
4. VP-IR-3472-1 Report of Addendum to Method Validation of “Determining Purity and Identity of -----
----- (b)(4)-----” (approved 28-FEB-11)
5. VP-FR-3526 Final Report of Validation of Determination of --- (b)(4) --- in IGIV Product by ----- (b)(4) -----
----- (approved 16-MAR-10)
6. SOP QC3148 Determining the Presence of --- (b)(4) --- in IGIV Product by ----- (b)(4) -----
(version 1, 1-FEB-11)
7. SOP QC3139 Determination of --- (b)(4) --- for Final Product Samples and Raw Materials (version 2, approved 26-APR-11)

E. Supporting Documents in BLA Amendment 13 (STN 125389/0.13) that were reviewed:

1. 1.11.1 Quality Information Amendment (dated 23-OCT-11) – Responses to 1-SEP-11 CR Letter
2. 2.3.S.2 Manufacture (dated 17-OCT-11)
3. 2.3.S.4 Control of Drug Substance (dated 24-OCT-11)
4. 2.3.S.5 Reference Standards or Materials (dated 24-OCT-11)
5. 2.3.P.2 Pharmaceutical Development (dated 14-OCT-11)
6. 2.3.P.3 Manufacture (dated 14-OCT-11)
7. 2.3.P.5 Control of Drug Product (dated 14-OCT-11)
8. 2.3.P.6 Reference Standards or Materials (dated 14-OCT-11)
9. 3.2.P.5.4 Batch Analyses (dated 20-OCT-11)
10. 3.2.P.5.6 Justification of Specification (dated 10-OCT-11)
11. 3.2.P.5.3.17 Diphtheria (dated 4-OCT-11)
12. 3.2.P.5.3.19 Particulate Matter (dated 29-SEP-11) – with reference to ----- (b)(4) ----- qualification report E041-2
13. 3.2.P.5.3.21 --- (b)(4) --- (dated 29-SEP-11)
14. SOP QC3139 Determination of --- (b)(4) --- for Final Product Samples and Raw Materials (revision 5, dated 16-SEP-11)
15. SOP (b)(4) --- Diphtheria Antitoxin Assay (BPC) (by ----- (b)(4) -----, effective date 11-NOV-11)
16. ----- (b)(4) ----- Qualification Executive Summary Validation No. ----- (b)(4) -----
----- (dated 19-APR-07)
17. VP-FR-3709-1 Validation of Method: Determination of --- (b)(4) --- for IGIV and -- (b)(4) -- Drug Substance and Drug
Product Samples
18. -----
----- (b)(4) -----

F. Supporting Documents in BLA Amendment 15 (STN 125389/0.15) that were reviewed:

1. 1.11.1 Quality Information Amendment (dated 23-JAN-12) – Responses to the 19-JAN-12 Information Request and 1-
SEP-11 CR Letter
2. 3.2.S.3.2 Impurities (dated 16-JAN-12) – note: new section 3.2.S.3.2.15 ----- (b)(4) ----- Factors
3. 3.2.S.4.2.13 Plasmin (dated 19-JAN-12)
4. 3.2.S.4.2.14 Plasminogen (19-JAN-12)
5. 3.2.S.4.3.13 Plasmin (dated 19-JAN-12)
6. 3.2.S.4.3.14 Plasminogen (dated 19-JAN-12)
7. SOP-T:EA-139-02/01: Determination of plasminogen activity in the ----- (b)(4) -----,
from Biotest AG (effective date of German version 9-DEC-11)
8. SOP-T:EA-140-02/00: Determination of plasmin activity in the ----- (b)(4) -----, from
Biotest AG (effective date of German version 21-APR-11)
9. SOP-T:EA-148-02/00: Determination of plasmin activity in Bivigam drug product and ----- (b)(4) ----- with the -----
----- (b)(4) -----, from Biotest AG (effective date of German version 213-JAN-12)
10. AB:E-00006/00 Determination of plasminogen activity in the ----- (b)(4) ----- (dated 9-JAN-12)
11. AB:E-00008/00 Determination of plasmin activity in Bivigam drug product and --- (b)(4) --- with the --- (b)(4) --- (dated
9-JAN-12)
12. IgA.pdf - Total IgA specification statistical analysis
13. ----- (b)(4) ----- specification analysis

G. Supporting Documents in BLA Amendment 19 (STN 125389/0.19) that were reviewed:

1. 1.11.1 Quality Information Amendment (dated 29-FEB-12) – Response to Information Request of 23-FEB-12

2. 2.3.S.2 Manufacture – which contains a revised Table 2.3.S.2-1 Biotest-IGIV Drug Substance Manufacturers (dated 27-FEB-12)
3. 3.2.S.2.1 Manufacturer(s) – which contains a revised Table 3.2.S.2.1-1 Biotest-IGIV Drug Substance Manufacturers (dated 27-FEB-12)

H. Supporting Documents in BLA Amendment 21 (STN 125389/0.21) that were reviewed:

1. Cover letter from -----(b)(4)----- (dated 27-FEB-12)
2. 1.11.1 Quality Information Amendment (dated 27-FEB-12) – Response to Information Request of 23-FEB-12
3. -----(b)(4)----- Addendum VI: Interim Validation Summary - Implementation of Hepatitis A --(b)(4)-- NAT Assay: HAV Genotypes (dated 9-AUG-11)
4. Hepatitis A Virus -----(b)(4)----- Assay package insert (----- (b)(4)-----)

I. Other Supporting Documents that were reviewed for this BLA submission:

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