



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%)	
on	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)----- -----
----- (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) -----	
----- (b)(4) -----	Meets 21 CFR 610.12 requirements	Meet -----
----- (b)(4) -----	Meets USP requirements at the 21 CFR 610.13 dose	Meet -----
----- (b)(4) -----	----- (b)(4) -----	
-----	≥ 0.60 x CBER Ref Std Lot 176 or ≥ internal std	
-----	----- (b)(4) -----	
-----	----- (b)(4) -----	-----
-----	----- (b)(4) -----	---(b)-----
-----	----- (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:

1. Contract testing laboratories: In the original BLA, there were slight differences in the contract testing laboratories that perform certain release tests for Bivigam and Nabi-HB. An information request was sent on 7-APR-11 to verify which testing laboratories were going to be used for testing appearance, sterility, -----(b)(4)----- purity (protein composition) and pyrogenicity The information provided by the sponsor in Amendment 9 was incorporated into Specification Tables 1 and 2 (see also Responses to IR questions 15a-c below, taken from Amendment 9 of the BLA submission, received 9-MAY-11).
2. Product specifications in general: Bivigam and Nabi-HB have similar specifications for drug substance and drug product, which are acceptable. Some Bivigam specifications appear to be based on those set for Nabi-HB, wherein the Nabi-HB limits were -----(b)(4)----- of Bivigam; the resulting limits for Bivigam were within the ranges seen with other licensed 10% IGIV products. However, there were some initial safety concerns regarding the following specifications: Total IgA, (b)(4), Polysorbate 80, hence more information requests were sent on these items (see below).
3. Total IgA specification – In the original BLA, no maximum limit specification was set for Bivigam; BPC only stated it as “Report Result”. In Amendment 9 (response to question 16b), BPC set an interim specification of $\leq 200 \mu\text{g/mL}$ based on the available data at that time (----- (b)(4)-----, and also committed to define the Total IgA specification based on a minimum of (b)(4) full-scale commercial lots. In Amendment 15, BPC followed up on their commitment by proposing the final drug substance specification for IgA as $\leq 200 \mu\text{g/mL}$, which is now based on the statistical analysis of the data from ----- (b)(4)----- . The result for clinical lot 100999 (--(b)(4)--) was determined to be an outlier and was excluded from the statistical analysis. The Total IgA levels of the --(b)(4)-- lots included in the statistical analysis ranged from --- (b)(4)--- and had a mean of ----- (b)(4)----- , therefore met the set specification (see IgA.pdf in Amendment 15, received 25-JAN-12).

- 4.
- (b)(4)
5. Polysorbate 80 specification: The Bivigam Polysorbate 80 (PS80) range is set 30x (*lower limit*) to 5x (*higher limit*) higher than Nabi-HB's. In addition, the amount of PS80 in Bivigam is 10x higher (the highest seen so far) when compared to the other IGIV products. The Pharm-Tox reviewer for this submission, Dr. Evi Struble, stated in her review memo that animal studies have shown that PS80 may carry a risk for cardiovascular, hepatic and renal adverse events. Following intravenous or intraperitoneal administration of PS80, some observations in animals included: a slight decrease in blood pressure, and an increase in liver enzyme levels and total bilirubin. Multiple information requests from FDA CBER regarding this issue were sent, however, in the end, BPC chose not to change the formulation of Bivigam given that these effects were not seen in the clinical study performed in support of this BLA. Instead, the sponsor stated that they will continue to monitor patients for cardiovascular, hepatic and renal adverse events as a postmarketing surveillance commitment (see Pharm-Tox Review Memo addendum of Dr. Evi Struble, dated 23-MAR-12).

- [illegible]

10.

(b)(4)

11.

(b)(4)

(b)(4)

(b)(4)

(b)(4)

12. Particulate Matter test method and specification: BPC contracted out the Particulate Matter testing of Bivigam to -----(b)(4)----- the same testing laboratory as that for Nabi-HB. The same method SOP will be used (SOP STP0011, version 7, dated 6-AUG-09, -----(b)(4)-----) and is performed according to the -----(b)(4)-----.
- Samples will be tested for particulate matter using the -----(b)(4)-----.
- (b)(4) ----- Bivigam will also have the same specification as that for -----(b)(4)----- has been inspected by the FDA and --(b)(4)-- has qualified their -----(b)(4)----- (see their qualification report submitted in Amendment 13, received 26-OCT-11).

13.

(b)(4)

-----.

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. -----

-----.

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 prior 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.

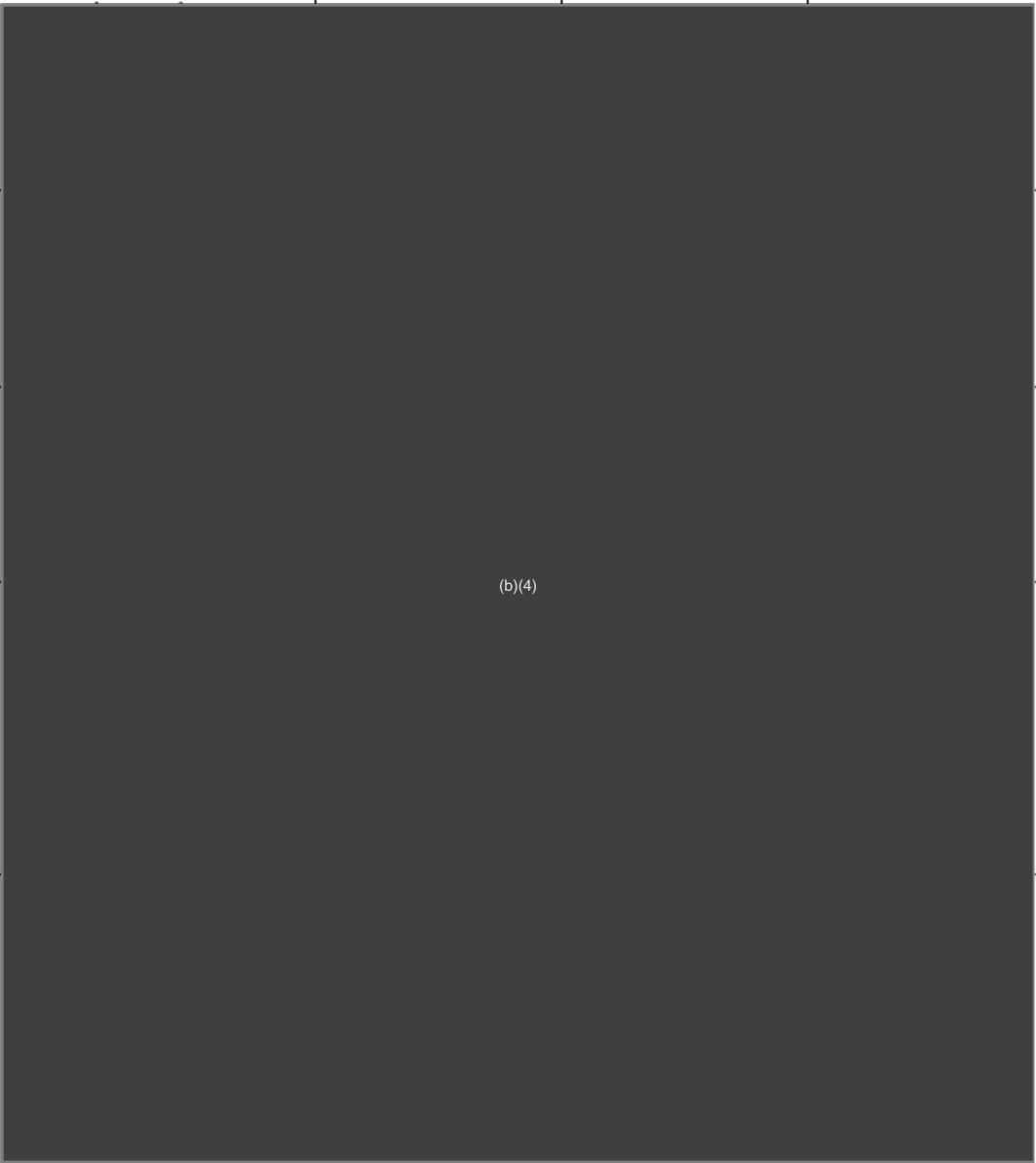
2. What is the current status with regards to screening HIV, HBV, HCV, parvovirus B19 and HAV in terms of minipool and manufacturing pool testing?

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				
HCV				
HIV				
Parvovirus B19				
HAV				

(b)(4)

* 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 10^4 IU/mL.

BPC confirmed that the B19 DNA limit for each manufacturing pool is set not to exceed 10^4 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.

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

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

- 18. Your diphtheria antitoxin specification is currently expressed in “IU/mL”, not in “units (U)/mL”. It is also not apparent in your method SOP about which reference standard you are using.**
- a. Please use the US Standard Diphtheria Antitoxin for revalidation and revise your specification such that it is expressed as “U/mL”. The minimum ratio for a 16.5% IgG solution is 2 U/mL; hence, the adjusted ratio for Biotest-IGIV should be approximately (b)(4) U/mL.**

BPC agreed to revalidate the assay for assessing diphtheria potency using the US Standard Diphtheria Antitoxin and revise the specification to express the result as “U/mL”. They also agreed to revise the specification so that the minimum ratio is (b)(4) IU/mL based on Biotest-IGIV’s 10% protein concentration.

Reviewer's Comment: BPC later determined that "x" in the ratio 16.5%: 2 U/mL = 10%: x U/mL was actually equivalent to (b)(4) (not (b)(4)), and adjusted their specification according to (b)(4) U/mL (see Responses to CR Items in Amendment 13 below). This correction is acceptable. The revised specification is comparable to those set for other 10% IGIV products.

- b. Please submit the revalidation study data and include the conversion ratio between IU and U.**

BPC said that the revalidation study will be initiated once they receive the US Standard Diphtheria Antitoxin and will be completed before testing the second set of Biotest-IGIV conformance lots. The revalidation study will include the conversion ratio between IU and U.

Reviewer's Comments: BPC sent an email on 16-JUN-11 with regards to the issue in 18b. BPC received the requested US Standard Diphtheria Antitoxin (Lot F-4509a) and realized that the standard is equine-based. They said that the (b)(4) that they validated for use to assess the potency of Bivigam for diphtheria antibodies is designed for testing human based samples and, therefore, cannot be used for testing equine based samples. As such, BPC said that they cannot revalidate the assay using the reference standard. The standard provided by the assay manufacturer was standardized to the NIBSC Standard 00/496. However, BPC said that NIBSC has agreed to perform a study to assess the comparability of the ---(b)(4)--- activity of the US Standard Diphtheria Antitoxin, NIBSC Standard 00/496, and the standard designed for use with the test kit being used at BPC. This would thus allow BPC to modify the reporting units for the assay as requested. They asked FDA if this revalidation approach would be acceptable.

However, their choice of test method was discussed further, resulting in FDA CBER saying that the using the (b)(4) is not acceptable. The -----(b)(4)----- on Immune Globulin recommends using the -----(b)(4)----- test for assessing anti-diphtheria antibody potency. An information request was sent to BPC on 3-AUG-11 recommending use of the ---(b)(4)--- test (if not tested in-house, this could be contracted to an outside testing laboratory that specializes in this type of testing). BPC agreed to -----(b)(4)----- assay and contracted out the testing to -----(b)(4)---. (see responses in Amendment 13).

- 19. You did not set specifications for albumin and plasmin/plasminogen impurities in the final product, stating that the levels are extremely low or undetectable. However, we recommend that you propose specifications for these two impurities in order to ensure safety and purity of Biotest-IGIV. In addition, please submit the supporting method SOPs and method validation studies.**

(b)(4)

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 10^4 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 10^4 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 “ $\geq 0.60 \times \text{Ref (176 CBER)}$ ”. Please take note that FDA CBER has allowed manufacturers to lower their anti-measles antibody specification from “ $\geq 0.60 \times \text{Ref (176 CBER)}$ ” to “ $\geq 0.48 \times \text{Ref (176 CBER)}$ ” 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 “ $\geq 0.60 \times \text{Ref (176 CBER)}$ ”.

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.

D. Responses to the 1-SEP-11 Complete Response (CR) Letter Items (received 26-OCT-11 in Amendment 13):

The CR letter items I covered were re-numbered as no. 3a-e here in this Amendment.

3. The validation of your Test Methods remains incomplete in that:

- a. the proposed ---(b)(4)--- assay -(b)(4)- to test the anti-Diphtheria potency of Bivigam does not meet CFR requirements. FDA recognizes that BPC has agreed to change the testing method to the recommended -----(b)(4)----- assay as per the (b)(4) Immune Globulin ---(b)(4)---, but this change has not been finalized.

BPC contracted out the anti-Diphtheria potency testing in --(b)(4)-- to the -----(b)(4)-----
------. They provided the (b)(4) method -----(b)(4)-----: Diphtheria Antitoxin Assay (BPC) in this
Amendment 13.

BPC readjusted the anti-Diphtheria potency specification to ----(b)(4)-----, instead of ----(b)(4)----, which was proposed earlier by FDA but was erroneously calculated, to account for Biotest-IGIV being a 10% IgG solution.

The second set of Biotest-IGIV conformance lots was tested using the -----(b)(4)----- assay as per the (b)(4) Immune Globulin ---(b)(4)---. The two conformance lots were reported as having anti-diphtheria antibody levels of ----(b)(4)---- (repeat testing was in progress at the time of reporting), which met the new readjusted potency limit (see the potency data collected so far in Section 3.2.P.5.4 Batch Analyses of Amendment 13).

Reviewer' Comments: (1) The method SOP lists the following reference standards and reagents that are used in the assay: the 1st WHO International Standard for Diphtheria Antitoxin, the US Standard Diphtheria Antitoxin for ----(b)(4)--- (CBER Standard), Diphtheria toxin Biological Reference Preparation (BRP) Batch 1 (EDQM), all of which are sufficient and acceptable. (b)(4) method is based on the -----(b)(4)----- for Diphtheria Antitoxin. It appears to be clearly written and detailed enough for analysts to follow. A section on test validity (retesting) is included.

(2) BPC stated in Section 3.2.P.5.3.17 Diphtheria that since the test is based on a compendial method and the CBER Standard Diphtheria Antitoxin or an equivalent standard is tested in each run and is used to calculate the assay value, a complete validation is not necessary.

- b. Your ---(b)(4)--- test method needs to be validated, preferably prior to the manufacture of the second set of conformance lots. The specification for ---(b)(4)--- (with minimum and maximum limits) remains to be set for the final drug product.

The ---(b)(4)--- test method was validated prior to the manufacture of the second set of conformance lots. A description of the test method (SOP QC3139), validation (VP-FR-3709-1), justification of the specification and standards were provided in this Amendment 13. The ---(b)(4)--- reference standard used in the test is a ----(b)(4)---- reference solution which is used to evaluate the performance of the ---(b)(4)---. It provides results that approximate the ----(b)(4)---- of human serum (see 2.3.P.6 Reference Standards or Materials).

Due to the timing of the filling of additional commercial lots, BPC committed to provide the proposed specification to FDA by January 2012 so that this could be based on data from clinical lots and more commercial-scale lots.

Reviewer's Comments: (1) The supporting documents that were provided were adequate and acceptable.

(2) -----

(b)(4)-----

e. The method SOPs and method validation reports related -----

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

-(b)(4).

Reviewer's Comments: -----

-(b)(4)

(2)

--(b)(4)

-(b)(4).

-(b)(4)

(3)

-(b)(4)

--(b)(4)

(4)

--(b)(4)

16.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 followed up to their commitment in Amendment 9 by setting the final Total IgA specification as “≤ 200 µg/mL” based on the data from (b)(4)- lots, which had residual IgA levels ranging from ----- (b)(4)-- (mean of -----(b)(4)-----).

Reviewer's Comment: This limit appears to be acceptable and could be comparable with the specification of another licensed 10% IGIV product, Gammagard Liquid, which has an IgA specification of "------(b)(4)-----", especially since the majority of the data from the Bivigam (b)(4) lots produced so far are within that approximate range.

F. Responses to the 23-FEB-12 Information Request (received 29-FEB-12 in Amendment 19 and received 1-MAR-12 in Amendment 21):

The -----(b)(4)----- Hepatitis A Virus -----(b)(4)----- Assay does not detect HAV genotype II and initially appeared to be the least sensitive of the three HAV NAT assays that BPC uses. Even though genotype II is rarely reported, FDA CBER recommends using HAV NAT assays that are sensitive enough to detect HAV genotypes I, II and III and their subtypes. On 23-FEB-12, FDA CBER sent a follow-up IR to -----(b)(4)----- through BPC requesting for more information regarding the improvement of their HAV NAT assay.

As requested, ---(b)(4)--- provided the following IR responses directly to FDA CBER in Amendment 21 (dated 27-FEB-12, received on 1-MAR-12):

1. With regards to the --(b)(4)-- Hepatitis A Virus ----(b)(4)--- Assay, please provide the following information:

a. the results of the additional studies conducted by ----(b)(4)---- to determine the level of sensitivity for the three HAV genotypes and their subtypes

(b)(4)

b. has the assay been improved such that it is now sensitive enough to detect HAV genotype II?

Due to the unavailability of the material, (b)(4)- said that they are unable to claim that their HAV NAT assay can detect genotype II (see cover letter of Amendment 21, from -----(b)(4)-----, dated 27-FEB-12).

c. the updated package insert which contains the revised assay sensitivity of ---(b)(4)-- for single pool samples

--(b)(4)-- submitted a copy of their updated package insert (revised as of 27-SEP-11) which now states the revised assay sensitivity of --(b)(4)---for single pool samples (see page 5 of 6 of the package insert). However, the genotypes detected still remains as genotypes IA, IB and III.

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)-----
-----)