



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

To: BLA STN 125350\0 File

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

Applicant: CSL Behring AG, Bern, Switzerland

Product: Immune Globulin Subcutaneous (Human), 20% Liquid, IgPro20
Proposed Trade name: Hizentra™

Subject: Midcycle CMC Review: Original BLA - Product Specifications, Analytical Procedures and Method Validations, Parvovirus B19 Nucleic Acid Testing, TSE Clearance Studies

Recommendation

An information request will be sent to the firm (see Letter-Ready Comments).

Background Summary

FDA CBER received on 30-APR-09 this original Biologics License Application (BLA) submission (dated 28-APR-09) from CSL Behring (CSLB), for Immune Globulin Subcutaneous (Human)(IGSC), 20% Liquid with the proposed trade name, "Hizentra™" (CSLB product code: "IgPro20"). IgPro20's proposed indication is for the treatment of patients with primary immunodeficiency diseases.

Pei Zhang, M.D., of LPD/DH/OBRR, HFM-345 is the chair of this BLA submission. My CMC review is limited only to the review of the Product Specifications (including Anti-Measles Antibodies, -----(b)(4)-----), Analytical Procedures and Method Validations, Parvovirus B19 Nucleic Acid Testing, Anti-measles Testing, and TSE Clearance Studies.

Supplement Review Summary

IgPro20 is a ready-to-use, sterile 20% (0.2 g/mL) protein, liquid preparation of human IgG for subcutaneous administration. IgPro20 is manufactured from large pools of human Source Plasma or recovered plasma by a combination of cold alcohol fractionation, octanoic acid precipitation, and anion exchange chromatography. The manufacturing process of IgPro20 is based on the manufacturing process of its parent product, Immune Globulin Intravenous (Human), 10% Liquid, IgPro10 or Privigen® (BLA STN 125201, licensed on 26-JUL-07). The manufacturing process of IgPro20 is identical to the FDA-licensed Privigen process up to the active substance solution step of IgPro10 (----(b)(4)----). In addition to the approved process: CSLB proposes to use: -----(b)(4)-----

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

After production of the active substance solution, -----(b)(4)-----, and preformulation, the protein solution is concentrated to the final protein concentration of 20%, resulting in IgPro20. IgPro20 is formulated with 250 mmol/L of L-proline (used as a stabilizer) and 10-30 mg/L polysorbate 80 and has a pH of 4.8. IgPro20 does not contain any sucrose or preservatives. Fill sizes include 5 mL (1 g), 10 mL (2 g), --(b)(4)--- and 20 mL (4 g). -(b)(4)- - glass infusion vials with ----- (b)(4) ----- stoppers will be used for filling.

IgPro20 will be manufactured at the licensed Bern, Switzerland facility, meanwhile the licensed -----(b)(4)----- facility will manufacture the ----- (b)(4) -----, which can be used as ----- (b)(4) ----- made in Bern. Both ----- (b)(4) ----- intermediates have been accepted as comparable (see IgPro10 original BLA).

I. Product Specifications, Analytical Procedures and Validations of Analytical Procedures:

A. Documents pertaining to this section that were submitted and reviewed – see Appendix

B. Comparison of Product Specifications and Analytical Procedures of IgPro20 vs. IgPro10

I compared the proposed product specifications of IgPro20 (see section 3.2.P.5.1) with the current product specifications of its parent product, IgPro10, in the following table:

Table 1: Proposed Specifications for IgPro20 (Hizentra) vs. Current Specifications for IgPro10 (Privigen)

Test	SOP No.	IgPro20 (Hizentra)	IgPro10 (Privigen)
Physicochemical Requirements			
Appearance	Q000228D Visual inspection	Clear and pale-yellow to light brown solution ----- (b)(4) ----- ----- -----	Clear or slightly opalescent and colorless or pale yellow solution
---(b)(4)---	Q000424D ----- (b)(4) ----- -----	---(b)(4)---	--(b)(4)---
Protein	Q000004D ----- (b)(4) ----- -----	-----(b)(4)-----	-----(b)(4)-----
L-Proline	Q000417D --(b)(4)---	210-290 mmol/L	210-290 mmol/L
Polysorbate 80	Q000480D (Hiz) ----- (b)(4) -----	10-30 mg/L	≤ 10 mg/L
-----(b)(4)-----	Q000087D (Hiz) ----- (b)(4) -----	---(b)(4)--- ----- -----	-----(b)(4)-----
Purity (IgG)	Q000033D ----- (b)(4) ----- ----- -----	≥ 98%	≥ 98%
--(b)(4)--	Q000033D	-(b)(4)-	-(b)(4)-
----- (b)(4) -----	Q000002D ----- (b)(4) ----- -----	-(b)(4)-	-(b)(4)-
----- (b)(4) ----- ----- -----	Q000002D (Pri)	---(b)(4)--- -----	-(b)(4)- -(b)(4)-

-(b)(4)-	Q000002D (Pri)	---(b)(4)---	-(b)(4)-
----- (b)(4) -----	Q000002D (Pri)	---(b)(4)---	-(b)(4)-
pH (1% protein in NaCl 0.9%)	Q000008D ----- (b)(4) ----- -----	4.60-5.20	4.60-5.00
---(b)(4)---	Q000060D (Pri)	----- (b)(4) ----- ----- -----	----- (b)(4) -----
Biological requirements			
Identity (Immunoelectrophoresis)	Q000034D ----- (b)(4) ----- -----	Detection of immunoglobulin G	Detection of immunoglobulin G
-(b)(4)-	Q000448D (Pri)	---(b)(4)---	-(b)(4)-
----- (b)(4) ----- -----	Q000152D ----- (b)(4) ----- ----- ----- -----	----- (b)(4) ----- -----	---(b)(4)---
Pyrogen test	Q000030D (Pri)	<i>None listed</i>	Pyrogen-free
Endotoxin test	Q000443D (Hiz) ----- (b)(4) ----- ----- method valid Feb 2007 based on -(b)(4)- ----- ----- -----	----- (b)(4) ----- -----, if using -(b)(4)- test, in Characterization of Impurities)	---(b)(4)---
Sterility	Q000027D ----- (b)(4) ----- ----- -----	No microbial growth detectable	No microbial growth detectable
General safety test	Q000032D In vivo test for abnormal toxicity based on CFR 610.11 - ---(b)(4)---	Pass	Pass
Immunological requirements			
---(b)(4)---	Q000432D ----- (b)(4) -----	---(b)(4)---	---(b)(4)---
Anti-Polio Type 1	Q000025D ----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
Anti-Measles	Q000452D ----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	Q000358D ---(b)(4)---	---(b)(4)---	---(b)(4)---
Diphtheria antitoxin	Q000157D ----- (b)(4) -----	---(b)(4)---	---(b)(4)---
----- (b)(4) -----	Q000328D ----- (b)(4) -----	---(b)(4)---	---(b)(4)---
----- (b)(4) -----	Q000403D (Pri) Q000479D (Hiz) ----- (b)(4) ----- <i>assay based on -(b)(4)-</i> ----- ----- -----	----- (b)(4) ----- -----	-(b)(4)-
----- (b)(4) -----	Q000403D (Pri) Q000479D (Hiz)	----- (b)(4) ----- -----	-(b)(4)-
-(b)(4)-	Q000378D ----- (b)(4) ----- ----- -----	----- (b)(4) ----- ----- -----	----- (b)(4) ----- ----- -----

	----- (b)(4) ----- ----- -----		
IgA	Q000430D ----- (b)(4) -----	≤ 50.0 mg/L	≤ 25.0 mg/L
-(b)(4)-	Q000462D (Hiz) ----- (b)(4) -----	-- (b)(4) ---	--- (b)(4) ---
Additional Tests (for stability testing only)			
--(b)(4)-	Q000007D (Hiz) ----- (b)(4) -----	----- (b)(4) -----	--- (b)(4) ---
Fc-Function	Q000074D (Hiz) ----- (b)(4) ----- -----	-(b)(4)-	-- (b)(4) ----
---(b)(4)----	Q000002D	-(b)(4)-	----- (b)(4) -----
---(b)(4)----	Q000002D	-(b)(4)-	----- (b)(4) -----
Other characteristics/ batch-related requirements			
Identity labeled product	Q000405D Finished package based on 21CFR 610.14	corresponds	corresponds
Visual inspection (100% of the bottles are controlled)	P034000D	<i>Not listed</i>	Bottles and closures are free of defects; aspect conforms to specification
Date of manufacture		<i>Not listed</i>	Date of final sterile filtration
Shelf Life		-(b)(4)- at 2-8 °C	2 years from date of manufacture
Storage Conditions		2-8 °C, protected from light	+2 °C to +25 °C, protected from light
Transport Conditions		<i>Not listed</i>	+2 °C to +25 °C, protected from light

*Lower antimeasles specification of **-(b)(4)-** x Ref (176 CBER) has already been approved for CSLB's other products: Privigen, Vivaglobin and Carimune NF.

**Shelf life of Privigen is 2 years from the date of manufacture. Date of manufacture is the date of final sterile filtration.

Reviewer's Comments:

1. The proposed specification for Hizentra's Appearance is listed as -----**(b)(4)**-----

(b)(4)-----

2. Compared to Privigen, several product specifications were not listed for Hizentra. The following need to be specifically set for Hizentra (with supporting justifications and validation reports for the methods used in measuring or testing):

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

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

- b. ----- (b)(4) ----- – These were not listed in the Physicochemical Requirements list, but were listed elsewhere (in the Stability Testing specifications) as “-(b)(4)- -----”. Hizentra’s proposed specifications for ----- (b)(4) ----- are -(b)(4)- higher than Privigen’s.

CSLB currently has an open PMC (#5) regarding Privigen’s specification for ----(b)(4)---- (end of shelf-life) (STN 125201/78, a Complete Response Letter was issued on 02-FEB-09). For PMC #5, CSLB committed ----- (b)(4) -----

Interestingly, Vivaglobin has the following approved specification for ----- (b)(4) -----.

- c. ----- (b)(4) -----
- d. ----- (b)(4) ----- – No SOP, method validation or specification were submitted.
- e. **Pyrogen test** – CSLB justified not setting the specification for the rabbit pyrogen test (RPT) because ----- (b)(4) -----

3. In addition, the following “other characteristics/batch-related requirements” were not defined or set: **visual inspection** (100% of the bottles are controlled), **date of manufacture**, and **transport conditions**.
4. On the -(b)(4)- specification: Hizentra’s proposed -(b)(4)- limit is more than 2x higher than that of Privigen (----- (b)(4) -----), however, it is identical to Vivaglobin’s specification, therefore it may be acceptable.
5. We need some clarification re: the correct set specification and method for the **Endotoxin Test** due to these conflicting numbers (see Table 2 below):

Table 2: Conflicting Reports of Hizentra’s Endotoxin Test Method and Specification

Listed in this section	Endotoxin Test Method	Endotoxin Test Specification
Biological Requirements	Q000443D (----- (b)(4) ----- method, valid Feb 2007)	---(b)(4)---
Characterization of Impurities	Q000081D (Impurities by -(b)(4)-).	----- (b)(4) -----

6. On the **Anti-Measles** specification, “-(b)(4)- x Ref (176 CBER)”:

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

Two (2) Pages Determined to be Non-Releasable: (b)(4)

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

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

8. On the **Diphtheria antitoxin** specification: For diphtheria potency, it is always units/mL, not IU/mL, if the US Standard is used. CSLB is using the WHO Standard (05/156) as the reference material for their assay. Will request that they validate their method using the US Standard and to provide the conversion ratio between IU and U.

C. Validation of Analytical Procedures

The majority of the SOPs submitted are updated versions of method protocols already in place for testing IgPro10, except for a couple of draft SOPs for testing polysorbate 80, ----- (b)(4) ----- . The corresponding method validation results have been summarized in Table 1, section 3.2.P.5.3 (see separate Data Appendix). Most of the validation studies were adequate and were performed in accordance with ICH Q2 (R1) and pharmacopoeial guidelines, except for the tests for general safety and appearance. Almost all methods met the acceptance criteria of the validations and appear to be suitable for testing IgPro20 (i.e., most of the linear ranges validated were able to detect the specified limits of IgPro20). However, I found some issues with the following methods/validations for:

1. **Polysorbate 80 (PS80) with** ----- (b)(4) ----- – The draft SOP and method validation data for this optimized --- (b)(4) --- method to measure PS80 were submitted in this IgPro20 BLA.
----- (b)(4) -----

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

3. **Anti-polio Type I** – For anti-polio Type 1, CBER’s required ratio is 0.28 x Ref (176 CBER). The required ratio for IgPro20 is listed as - (b)(4) - x Ref (176 CBER), which is acceptable, since the adjusted ratio is ----- (b)(4) ----- . However, the validation data are expressed in IU/mL. (see validation report no. 05002.12.- (b)(4) -.011_01, approved 30-APR-08, section 3.2.P.5.3 Attachment 13). A formula for calculating the titer in terms of x Ref 176 CBER is included in the method SOP Q000025D_17 (English translation approved 10-FEB-09, section 3.2.P.5.2, Attachment 14), however, the validation results were not converted to “x Ref 176 CBER”. Will request that the data be converted to “x Ref 176 CBER” for easier comparison.

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

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

II. Parvovirus B19 Nucleic Acid Testing (NAT) of Plasma Manufacturing Pools -----~~(b)(4)~~---

For this IgPro20 BLA, CSLB submitted the method summaries and validation reports for the Parvovirus B19 NAT methods of the -----~~(b)(4)~~-----.

However, it was not clear which B19 NAT method(s) will be used for testing ---~~(b)(4)~~-- and manufacturing pools (and for which type of plasma). In the Description section of the draft package insert, CSLB stated that the “limit for B19V in the fractionation pool is set not to exceed 10^4 IU of B19V DNA per mL” which complies with FDA CBER’s B19 NAT recommendations (see FDA Guidance for Industry: Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-derived Products, effective July 2009).

Reviewer’s Comments: --~~(b)(4)~~-- and manufacturing pool B19 NAT testing of Source Plasma for IgPro10 production are performed by -----~~(b)(4)~~-----, respectively (STNs 125201/29, 125201/60, 125201/8). Meanwhile, --~~(b)(4)~~-- B19 NAT testing of recovered plasma for IgPro10 production is performed by the --~~(b)(4)~~-- -----, while -----~~(b)(4)~~----- do the manufacturing pool testing of recovered plasma (STN 125201/117). The inclusion of the --~~(b)(4)~~-- B19 NAT documents here in this IgPro20 BLA marks the first time CSLB has indicated that they intend to use --~~(b)(4)~~-- as a B19 contract testing lab.

III. TSE Clearance Studies

Three manufacturing steps were monitored for their TSE clearance potential: the octanoic acid (OA) fractionation step, the subsequent depth filtration step -----~~(b)(4)~~-----, and the virus filtration step (-----~~(b)(4)~~-----). In these TSE clearance studies, 3 different prion spike preparations (-----~~(b)(4)~~-----) were used as well as 3 different quantitation methods (-----~~(b)(4)~~-----). Table 4 below lists the test facilities where the different TSE assays were performed.

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

[~~(b)(4)~~ **]**

In the Description section of the IgPro20 draft package insert (page 16), CSLB claims that TSE clearance factors are **$\geq 6.4 \log_{10}$ from OA fractionation, $2.6 \log_{10}$ from depth filtration and $\geq 5.8 \log_{10}$ from virus filtration.** These are the LRF values calculated primarily from the -----~~(b)(4)~~----- studies (see Table 5 below). All 3 steps significantly reduced the 3 different prion spike preparations, resulting in an overall log reduction factor of **$> 14 \log_{10}$** . According to CSLB, comparable results were obtained using the 3 assays.

Reviewer’s Comments: (1) Only claims of infectivity clearance are allowed by FDA CBER at this time, therefore TSE clearance claims for IgPro20 should be based only on the --~~(b)(4)~~-- study reports that were submitted. The -----~~(b)(4)~~-----

----- (b)(4) ----- . Results from the TSE studies are summarized in the Tables 5, 6 and 7 below.

(2) CSLB stated that no component in IgPro20 is derived from ruminant material. TSE and vCJD risk assessment studies were also provided in this submission that evaluated the materials of animal origin used during IgPro20 production, plasma source, reduction capacity of the manufacturing process and sanitization of the equipment (Attachments 58 and 60). The studies concluded that risks of TSE and vCJD infections were negligible.

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

A. TSE study documents that were submitted and reviewed – see Appendix

B. Review of TSE Clearance Studies

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

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

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

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

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

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

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

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

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

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

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

LETTER-READY COMMENTS

1. The proposed specification for Appearance, "...*light brown solution* ----- (b)(4) -----

----- . Please provide an appropriate justification for the lowering of this
specification. Also, please provide additional information on the following related items:

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

2. Please provide appropriate justifications for the lack of final container specifications for the following
physicochemical and biological requirements:

- a. ----(b)(4)-----
- b. -----(b)(4)----- (at release and at end of shelf life)
- c. ----(b)(4)---- (upper and lower limits)
- d. -----(b)(4)-----
- e. Pyrogen test

In addition, please provide the method SOPs and validation reports for each of the test methods used.

3. Please specify the following "other characteristics/batch-related requirements":

- a. Visual inspection (100% of the bottles are controlled)
- b. Date of manufacture
- c. Transport conditions

- c. SOP Q000424D_05: -----(b)(4)----- (version 5, valid 17-APR-07)(section 3.2.P.5.2, Attachment 01)
- d. SOP Q000004D_23: Protein --(b)(4)- (version 23, signed 20-FEB-09)(section 3.2.P.5.2, Attachment 02) – version 21 is validated but not version 23, several minor additions and adjustments in version 23
- e. SOP Q000417D_09: -----(b)(4)----- (version 9, signed 19-FEB-09)(section 3.2.P.5.2, Attachment 03) - version 06 is validated 29-JAN-07, implementation of new additional control -(b)(4)-
- f. SOP Q000480D_Draft01: Polysorbate 80 with -----(b)(4)----- (Draft 01, signed 10-FEB-09) validated 24-NOV-08 using IgPro20 final product without PS80, spiked with ----(b)(4)---- PS80 (section 3.2.P.5.2, Attachment 04)
- g. SOP Q000033D_14: Purity (----- (b)(4)-----) (version 14, valid 20-JUL-07) (section 3.2.P.5.2, Attachment 05) validated 30-APR-08
- h. SOP Q000002D_14: -----(b)(4)----- (version 14, signed 19-FEB-09) (section 3.2.P.5.2, Attachment 06)
- i. SOP Q000008D_06: pH of protein solutions (version 06, signed 19-FEB-09) (section 3.2.P.5.2, Attachment 07)
- j. SOP Q000034D_09: -----(b)(4)----- (version 09, valid 12-MAR-07) (section 3.2.P.5.2, Attachment 08)
- k. SOP Q000152D_11: -----(b)(4)----- (version 11, valid 25-JUN-07) (section 3.2.P.5.2, Attachment 09)
- l. SOP Q000443D_04: Bacterial endotoxins: -----(b)(4)----- method (version 04, valid 5-FEB-07) (section 3.2.P.5.2, Attachment 10)
- m. SOP Q000027D_12: Sterility: -----(b)(4)----- method (version 12, valid 3-JAN-06) (English translation of original German version, signed 26-JUL-06)(section 3.2.P.5.2, Attachment 11)
- n. SOP Q000032D_10: Toxicity: -----(b)(4)----- (version 10, signed 18-FEB-09) (section 3.2.P.5.2, Attachment 12)
- o. SOP Q000432D_07: -----(b)(4)----- (version 07, valid 25-AUG-08) (section 3.2.P.5.2, Attachment 13)
- p. SOP Q000025D_17: Anti-polio antibody (----(b)(4)----- test) (version 17, signed 10-FEB-09) (section 3.2.P.5.2, Attachment 14)
- q. SOP Q000452D_02: Determination of measles antibodies by the -----(b)(4)----- test (version 02, signed 10-FEB-09) (section 3.2.P.5.2, Attachment 15)
- r. SOP Q000358D_05: -----(b)(4)----- (version 05, valid 10-MAR-08) (section 3.2.P.5.2, Attachment 16)
- s. SOP Q000157D_13: Anti-diphtheria-toxin antibody (----(b)(4)---- method) (version 13, signed 10-FEB-09) (section 3.2.P.5.2, Attachment 17)
- t. SOP Q000328D_13: Anti-parvovirus B19: -----(b)(4)----- (version 13, signed 30-JAN-09) (section 3.2.P.5.2, Attachment 18)
- u. SOP Q000479D_Draft01: Determination of -----(b)(4)----- of the IgG and -(b)(4)- type in --- (b)(4)--- ----- (Draft 01, signed 11-FEB-09) (section 3.2.P.5.2, Attachment 19)
- v. SOP Q000378D_04: -(b)(4)- antibody screening with the -----(b)(4)----- test according to the -(b)(4)--- (version 04, valid 30-OCT-06) (English translation of original German version, signed 2-NOV-06)(section 3.2.P.5.2, Attachment 20)
- w. SOP Q000430D_04: IgA----- (b)(4)----- (version 04, valid 7-APR-08) (section 3.2.P.5.2, Attachment 21)
- x. SOP Q000462D_03: -----(b)(4)----- (version 03, signed 24-MAR-09) (section 3.2.P.5.2, Attachment 22)
- y. SOP Q000007D_04: -(b)(4)- (version 04, valid 20-FEB-06) (English translation of original German version, signed 17-JUL-06)(section 3.2.P.5.2, Attachment 23)
- z. SOP Q000074D_09: Fc-function test (version 09, valid 5-SEP-05) (English translation of original German version, signed 18-JUL-06)(section 3.2.P.5.2, Attachment 24)
- aa. SOP Q000405D_05: Immunoglobulin liquid identity test (----- (b)(4)-----) (version 05, signed 2-APR-09) (section 3.2.P.5.2, Attachment 25)
- bb. SOP Q000228D_12: Visual aspect of solutions, lyophilized products and reconstitutions (version 12, signed 11-FEB-09) (section 3.2.P.5.2, Attachment 26)
- cc. 3.2.P.5.3 Validation of Analytical Procedures – contains tables listing validation results of analytical procedures used for testing the final product

- dd. 07004.00.-(b)(4)-.001_01 Validation Report for Analytical Method: -----(b)(4)-----
----- (approved 07-JUN-07)(section 3.2.P.5.3, Attachment 01)
- ee. 05002.12.-(b)(4)-.021_01 Validation Report for Analytical Method: Protein -----(b)(4)-----
(approved 25-JAN-08)(section 3.2.P.5.3, Attachment 02)
- ff. 05002.12.-(b)(4)-.018_01 Validation Report for Analytical Method: Proline (-(b)(4)-)(approved 22-JUN-07)(section 3.2.P.5.3, Attachment 03)
- gg. 05002.12.-(b)(4)-.029_02 Validation Report for Analytical Method: Polysorbate 80 (---(b)(4)---)(approved 3-DEC-08)(section 3.2.P.5.3, Attachment 04)
- hh. 05002.12.-(b)(4)-.014_01 Validation Report for Analytical Method: Purity (IgG) by -----(b)(4)-----
----- (approved 30-APR-08)(section 3.2.P.5.3, Attachment 05)
- ii. 05002.12.-(b)(4)-.019_01 Validation Report for Analytical Method: -----(b)(4)----- (approved 20-MAR-08)(section 3.2.P.5.3, Attachment 06)
- jj. 05002.12.-(b)(4)-.020_01 Validation Report for Analytical Method: pH 1% (approved 22-DEC-06)(section 3.2.P.5.3, Attachment 07)
- kk. 05002.12.-(b)(4)-.013_01 Validation Report for Analytical Method: Identity/----- (b)(4)-----
(approved 11-MAR-08)(section 3.2.P.5.3, Attachment 08)
- ll. 05002.12.-(b)(4)-.039_01 Validation Report for Analytical Method: -----(b)(4)-----
----- (approved 1-DEC-08)(section 3.2.P.5.3, Attachment 09)
- mm. 05002.12.-(b)(4)-.023_01 Validation Report for Analytical Method: -----(b)(4)-----
----- (approved 28-JUN-07)(section 3.2.P.5.3, Attachment 10)
- nn. 05002.12.-(b)(4)-.001_01 Validation Report for Analytical Method: Sterility Test (approved 26-APR-06)(section 3.2.P.5.3, Attachment 11)
- oo. 05002.12.-(b)(4)-.008_02 Validation Report for Analytical Method: -----(b)(4)----- (approved 06-FEB-09)(section 3.2.P.5.3, Attachment 12)
- pp. 05002.12.-(b)(4)-.011_02 Validation Report for Analytical Method: Anti-Polio Antibodies (approved 30-APR-09)(section 3.2.P.5.3, Attachment 13)
- qq. 05002.12.-(b)(4)-.009_01 Validation Report for Analytical Method: Anti-Measles (-(b)(4)-) (approved 11-NOV-08)(section 3.2.P.5.3, Attachment 14)
- rr. 05002.12.-(b)(4)-.028_01 Validation Report for Analytical Method: -----(b)(4)-----
(approved 4-JUL-08)(section 3.2.P.5.3, Attachment 15)
- ss. 05002.12.-(b)(4)-.012_01 Validation Report for Analytical Method: Diphteria Antitoxin (approved 30-APR-08)(section 3.2.P.5.3, Attachment 16)
- tt. 05002.12.-(b)(4)-.010_02 Validation Report for Analytical Method: -----(b)(4)----- (approved 30-JAN-08)(section 3.2.P.5.3, Attachment 17)
- uu. 05002.12.-(b)(4)-.024_01 Validation Report for Analytical Method: -----(b)(4)-----
(approved 27-JAN-09)(section 3.2.P.5.3, Attachment 18)
- vv. 05002.12.-(b)(4)-.025_01 Validation Report for Analytical Method: -----(b)(4)-----
----- (approved 20-FEB-08)(section 3.2.P.5.3, Attachment 19)
- ww. 05002.12.-(b)(4)-.026_01 Validation Report for Analytical Method: IgA--(b)(4)- (approved 13-OCT-08)(section 3.2.P.5.3, Attachment 20)
- xx. 08080.00.-(b)(4)-.001_01 Validation Report for Analytical Method: ----(b)(4)--- (approved 16-DEC-08)(section 3.2.P.5.3, Attachment 21)
- yy. 05002.12.-(b)(4)-.017_01 Validation Report for Analytical Method: -(b)(4)- (approved 05-APR-07)(section 3.2.P.5.3, Attachment 22)
- zz. 05002.12.-(b)(4)-.022_01 Validation Report for Analytical Method: Fc Function (-(b)(4)-) (approved 13-JAN-09)(section 3.2.P.5.3, Attachment 23)
- aaa. 05002.12.-(b)(4)-.043_01 Validation Report for Analytical Method: Identity test -----(b)(4)-----
(approved 6-MAR-09)(section 3.2.P.5.3, Attachment 24)

2. Parvovirus B19 NAT of Plasma Manufacturing Pools -----(b)(4)-----

- a. Analytical Procedure Summary B19 -----(b)(4)----- (plasma pools) (section 3.2.S.2.3, Attachment 07)
- b. 05149.00.-(b)(4)-.001_05 Validation Report for Analytical Method: B19--(b)(4)- testing (performed at -(b)(4)-)
(approved 9-APR-08)(section 3.2.S.2.3, Attachment 08)
- c. Analytical Procedure Summary B19 -----(b)(4)----- (section 3.2.S.2.3, Attachment 13)

- d. Validation Reports for -----(b)(4)----- (section 3.2.S.2.3, Attachment 14)
- e. Analytical Procedure Summary B19 -(b)(4)- Method (plasma pools) B19 FDQA v1 (section 3.2.S.2.3, Attachment 21)
- f. T.18.47-01: Validation of the Parvovirus B19 -----(b)(4)----- Assay version 2 (B19 FDQA v2) (valid 19-DEC-08)(section 3.2.S.2.3, Attachment 22),.

3. TSE Clearance Studies

- a. -(b)(4)-_00772: Comparability of the scale down process sequence OA-fractionation (approved 21-MAY-03)(section 3.2.A.2, Attachment 01)
- b. -(b)(4)-_1497: Comparability of the scale down process sequence OA-fractionation for -----(b)(4)----- (approved 24-JAN-06)(section 3.2.A.2, Attachment 02)
- c. -(b)(4)-_00875: Comparability of the scale down process sequence combined -(b)(4)- filtration (approved 18-SEP-03)(section 3.2.A.2, Attachment 03)
- d. -(b)(4)-_00963: Comparability of the scale down process sequence nanofiltration (approved 16-DEC-03)(section 3.2.A.2, Attachment 04)
- e. ZLB 03_029: Partitioning of TSE infectivity during the octanoic acid fractionation in the combined CSL-ZLB IVIG process (section 3.2.A.2, Attachment 48)
- f. ZLB 03_050: Partitioning of TSE infectivity during the -----(b)(4)----- filtration of combined CSL-ZLB IVIG process (section 3.2.A.2, Attachment 49)
- g. ZLB 03_058: Partitioning of TSE infectivity during nanofiltration in the combined CSL-ZLB IVIG process (section 3.2.A.2, Attachment 50)
- h. 04_05-(b)(4)-: Partitioning of TSE infectivity during the IgPro10 manufacturing process of CSL Behring, Berne (section 3.2.A.2, Attachment 51)
- i. -(b)(4)--IgPro10-02: Evaluation of prion removal by octanoic acid fractionation in the IgPro10 manufacturing process (section 3.2.A.2, Attachment 52)
- j. -(b)(4)--IgPro10-01: Evaluation of prion removal by -----(b)(4)----- filtration in the IgPro10 manufacturing process (section 3.2.A.2, Attachment 53)
- k. -(b)(4)--IgPro10-03: Evaluation of prion removal by nanofiltration in the IgPro10 manufacturing process (section 3.2.A.2, Attachment 54)
- l. -(b)(4)--IgPro10-04: Evaluation of prion removal by octanoic acid fractionation in the IgPro10 manufacturing process using -----(b)(4)----- as starting material (section 3.2.A.2, Attachment 55)
- m. -(b)(4)--IgPro10-01: Removal of prions by the IgPro10 manufacturing process (section 3.2.A.2, Attachment 56)
- n. Normal Human Immunoglobulin 20% solution for subcutaneous administration: TSE risk assessment (section 3.2.A.2, Attachment 58)
- o. Normal Human Immunoglobulin 20% solution for subcutaneous administration: vCJD risk assessment (section 3.2.A.2, Attachment 60)

Six (6) Pages Determined to be Non-Releasable: (b)(4)