



## Executive Summary

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which was based on the stability data of two clinical lots that were stored for 18 months (see D. Frazier’s review memo).

Other Product Specifications that needed to be set were for -----(b)(4)-----, and pyrogen testing. CSLB followed FDA CBER’s recommendation and set the IgPro20 -(b)(4)- specification for -----(b)(4)---- based on 18 lots that were tested using a newly validated method. CSLB reasoned that no -(b)(4)- specification had been set for their other IGSC product, Vivaglobin, however, FDA CBER decided that IgPro20’s -(b)(4)- levels should be monitored and that a limit should be set due to the product’s -----(b)(4)----. CSLB also requested for replacement of the Rabbit Pyrogen Test with the -----(b)(4)----- Test, however, FDA CBER found their comparability data to be insufficient due to the lack of a positive control lot, therefore, recommended to keep the Rabbit Pyrogen Test in place until they can provide better supporting data.

CSLB agreed to commit to 5 Post-Marketing Commitments (PMC), 3 of which are related to this review: -(b)(4)-  
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**Recommendation**

Approval, with the following Post-Marketing Commitments related to this review (see below)

**Post-Marketing Commitments (PMC) agreed to by CSLB on 4-FEB-2010**

A teleconference was held between FDA CBER and CSLB on 4-FEB-10, where CSLB agreed to do the following requested PMCs that are covered in this review (see 4-FEB-10 Meeting Minutes):

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Within three months following the implementation of this new version of the -----(b)(4)-----, CSL Behring will submit the necessary validation data supporting these changes in a Changes Being Effectuated in 30 Days (CBE-30) supplement.

**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 (PID).

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, B19 and -(b)(4)- NAT, 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 FDA-approved manufacturing process of its parent product, Immune Globulin Intravenous (Human), 10% Liquid, IgPro10 or Privigen® (BLA STN 125201, licensed on 26-JUL-07), which is identical up to the active substance solution step of IgPro10 (----(b)(4)----). In addition to the approved process, CSLB included the following for IgPro20: -----(b)(4)-----  
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After production of the ----(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 are 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)----- 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, no. 1

#### **B. Product Specifications and Analytical Procedures of IgPro20**

1. Comparison of the product specifications of IgPro20 (Section 3.2.P.5.1) with the current product specifications of its parent product, IgPro10 (see Table 1 below):

IgPro20 specifications and analytical procedures were provided, clarified or revised in the responses to FDA CBER’s information requests (IR) sent on 5-NOV-09, 23-DEC-09 and 4-FEB-10.

**Table 1:** Final Product Specifications for IgPro20 (Hizentra) vs. IgPro10 (Privigen)

Test	SOP No.	IgPro20 (Hizentra)	IgPro10 (Privigen)
<b><i>Physicochemical Requirements</i></b>			
<b>Appearance</b>	Q000228D Visual inspection	Clear and pale-yellow to light brown solution (at lot release); ------(b)(4)----- ----- -----	Clear or slightly opalescent and colorless or pale yellow solution

Test	SOP No.	IgPro20 (Hizentra)	IgPro10 (Privigen)
----- (b)(4) -----	Q000424D ----- (b)(4) ----- -----	-- (b)(4) --	-- (b)(4) --
<b>Protein</b>	Q000004D ----- (b)(4) ----- -----	180.0-220.0 g/L	90.0-110.0 g/L
<b>L-Proline</b>	Q000417D --- (b)(4) ---	210-290 mmol/L	210-290 mmol/L
<b>Polysorbate 80 (PS80)</b>	Q000480D - (b)(4) - -----	10-30 mg/L	≤ 10 mg/L
----- (b)(4) -----	Q000482D - (b)(4) - -----	--- (b)(4) ---	--- (b)(4) ---
<b>Purity (IgG)</b>	Q000033D ----- (b)(4) ----- ----- -----	≥ 98%	≥ 98%
-- (b)(4) --	Q000033D	- (b)(4) -	- (b)(4) -
----- (b)(4) -----	Q000002D ----- (b)(4) ----- -----	- (b)(4) -	- (b)(4) -
--- (b)(4) ---	Q000002D	- (b)(4) -	----- (b)(4) ----- -----
----- (b)(4) ----- -----	Q000002D	- (b)(4) -	--- (b)(4) ---
- (b)(4) -	Q000002D	----- (b)(4) -----	- (b)(4) -
----- (b)(4) -----	Q000002D	----- (b)(4) ----- -----	- (b)(4) -
<b>pH</b> (1% protein in NaCl 0.9%)	Q000008D ----- (b)(4) ----- -----	4.60-5.20	4.60-5.00
---- (b)(4) ---	---- (b)(4) ----	----- (b)(4) -----	----- (b)(4) -----
<b>Biological requirements</b>			
<b>Identity</b> (Immunoelectrophoresis)	Q000034D ----- (b)(4) ----- -----	Detection of immunoglobulin G	Detection of immunoglobulin G
-- (b)(4) --	---- (b)(4) ----	----- (b)(4) -----	- (b)(4) -
----- (b)(4) ----- -----	Q000152D ----- (b)(4) ----- ----- ----- -----	----- (b)(4) ----- -----	--- (b)(4) ---
<b>Pyrogen test</b>	Q000030D (Pri) based on --- (b)(4) ---	Pass	Pyrogen-free
<b>Endotoxin test</b>	Q000443D (Hiz) ----- (b)(4) ----- ----- method valid Feb 2007 based on - (b)(4) - -----	--- (b)(4) ---	<i>None listed</i>
<b>Sterility</b>	Q000027D ----- (b)(4) ----- based on ---- (b)(4) ---- -----	No microbial growth detectable	No microbial growth detectable
<b>General safety test</b>	Q000032D <i>In vivo</i> test for abnormal toxicity based on CFR 610.11 ----- (b)(4) -----	Pass	Pass

Test	SOP No.	IgPro20 (Hizentra)	IgPro10 (Privigen)
<b>Immunological requirements</b>			
---(b)(4)--	Q000432D (b)(4)-----	----(b)(4)----	----(b)(4)----
<b>Anti-Polio Type 1</b>	Q000025D ----- (b)(4)-----	-(b)(4)- x Ref (176 CBER)	-(b)(4)- x Ref (176 CBER)
<b>Anti-Measles</b>	Q000452D ----- (b)(4)-----	-(b)(4)- x Ref (176 CBER)	-(b)(4)- x Ref (176 CBER)
----- (b)(4)-----	Q000358D -----(b)(4)----	-----(b)(4)----	-----(b)(4)----
<b>Diphtheria antitoxin</b>	Q000157D ----- (b)(4)-----	-(b)(4)- IU/mL	-(b)(4)- IU/mL
----- (b)(4)-----	Q000328D ----- (b)(4)-----	-----(b)(4)----	-----(b)(4)----
----- (b)(4)-----	Q000403D (Pri) Q000479D (Hiz)	----- (b)(4)----- -----	-(b)(4)-
----- (b)(4)-----	----- (b)(4)----- ----- -----	----- (b)(4)----- -----	-(b)(4)-
-(b)(4)-	Q000378D ----- (b)(4)----- ----- ----- -----	----- (b)(4)----- ----- -----	----- (b)(4)----- ----- -----
<b>IgA</b>	Q000430D -----(b)(4)----	≤ 50.0 mg/L	≤ 25.0 mg/L
-(b)(4)-	Q000462D (Hiz) ----- (b)(4)-----	---(b)(4)---	---(b)(4)---
<b>Additional Tests (for stability testing only)</b>			
-(b)(4)--	Q000007D (Hiz) ----- (b)(4)-----	----- (b)(4)-----	---(b)(4)---
<b>Fc-Function</b>	Q000074D (Hiz) ----- (b)(4)----- -----	-(b)(4)-	---(b)(4)---
<b>Other characteristics/ batch-related requirements</b>			
<b>Identity labeled product</b>	Q000405D Finished package in accordance with 21CFR 610.14	Corresponds	Corresponds
<b>Visual inspection (100% of the bottles are controlled)</b>	P034000D	Bottles and closures are free of defects; aspect conforms to specification	Bottles and closures are free of defects; aspect conforms to specification
<b>Date of manufacture</b>		Date of final sterile filtration	Date of final sterile filtration
<b>Shelf Life</b>		18 months from date of manufacture	2 years from date of manufacture
<b>Storage Conditions</b>		+2 °C to +25 °C, protected from light	+2 °C to +25 °C, protected from light
<b>Transport Conditions</b>		+2 °C to +25 °C, protected from light	+2 °C to +25 °C, protected from light

2. Special product specification issues that were reviewed:

a. Appearance specification:



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- ii. Study Report ZLB04\_009CR Measles Sub-Study: “A Phase III, Open-Label, Prospective, Multicenter Study of the Efficacy, Tolerability, Safety and Pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20, in Subjects with Primary Immunodeficiency (PID)” (version 1.0, dated 30-MAR-09)(Section 5.3.3.2.1) – A pharmacokinetic study was undertaken to investigate the batch potency and dose response relation of anti-measles antibodies in PID patients treated with IgPro20. This study report contains IgG trough level and anti-measles titer data taken from a subgroup of 18 PID patients participating in the pharmacokinetic component of ZLB04\_009CR clinical study (see Listings 1 and 2, pages 15-18 of the report). These patients were treated with 4 weekly infusions of IgPro20 prior to blood sampling at Week 28 ± 1 (steady state). The 4 clinical lots used had anti-measles potency ratios ranging from 0.6 to 1.4 x Ref (CBER 176) (Table 2, page 10 of 18). Anti-measles IgG serum concentrations were analyzed by the -----(b)(4)-----  
----- using a -----(b)(4)-----  
----- All subjects considered in this sub-study were kept safely above the protective level of 0.24 IU/mL after repeated dosing with IgPro20. This also held true if the serum titers were shrunk according to the hypothetical lot potencies of -(b)(4)- or -(b)(4)- x US Ref Ig. CSLB concluded that a lot specification lowered to -(b)(4)- or -(b)(4)- x US Ref Ig would provide protection against measles infection to PID subjects treated with repeated doses of IgPro20.

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*The information provided by CSLB to support this request for a “lower” anti-measles specification is only acceptable with one PMC and revisions in the package insert. Both were committed on Feb 26, 2010. The PMC is “To report measles in a PIDD patient as a 15-day adverse event report.”*

For the package insert, the following changes were made under **Measles Exposure in DOSAGE AND ADMINISTRATION**:

*“If a patient is at risk of measles exposure (i.e., due to an outbreak in the US or travel to endemic areas outside of the US), the weekly Hizentra dose should be a minimum of 200 mg/kg body weight for two consecutive weeks. If a patient has been exposed to measles, ensure this minimum dose is administered as soon as possible after exposure.”*

- c. -----(b)(4)----- analytical procedure and specification:

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### 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 few new SOPs for testing -(b)(4)-, polysorbate 80 (PS80), -----(b)(4)-----  
 ----- Most of the corresponding method validation results were summarized in Table 1, Section 3.2.P.5.3, except for the -(b)(4)- and Diphtheria Antitoxin test validation results, which were later provided on 29-JAN-10, see IR Responses below). 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. For most of the methods, the validation results met the acceptance criteria and appeared to be suitable for testing IgPro20 (i.e., most of the linear ranges validated were able to detect the specified limits of IgPro20). There were some minor issues with the method validations of tests for -(b)(4)-, Anti-Polio Type 1, ----- (b)(4) ----- that were brought to CSLB’s attention and resolved (see responses to 5-NOV-09 and 23-DEC-09 IRs below).

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

CSLB submitted the method summaries and validation reports for the Parvovirus B19 NAT methods of the ----- (b)(4) -----  
 ----- (see list of documents that were submitted and reviewed in Appendix, no. 2). CSLB clarified in their response to the 5-NOV-09 IR the following testing laboratory assignments:

**Table 3:** Laboratories for B19V DNA testing of manufacturing pools and ---(b)(4)--- for IgPro20

Laboratory	Manufacturing Pool Testing	(b)(4)-----
----(b)(4)----	Routine Testing Lab	--(b)(4)---
----(b)(4)-----	Back-up Testing Lab (first-line)	(b)(4)-----
----(b)(4)-----	Back-up Testing Lab (second-line)	--(b)(4)---
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The method SOPs and method validations of these testing laboratories have been reviewed previously and were found acceptable by FDA CBER (3 of them in connection with IgPro10), except for ----(b)(4)---. CSLB



provided more information on ----(b)(4)---- B19 NAT method in their response to the 23-DEC-09 IR (see Section B below). --(b)(4)-- B19 NAT method has also been reviewed and approved previously for --(b)(4)-- plasma-derived products, but this marks the first time CSLB has indicated that they intend to use --(b)(4)-- as a B19 contract testing lab.

In the Description section of the IgPro20 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).

### 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.

**Table 4:** Test facilities for TSE determinations

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In the Description section of the IgPro20 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) which are acceptable. 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. Results from the TSE studies are summarized in the Tables 5, 6 and 7 below.

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.

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**A. TSE study documents that were submitted and reviewed** – see Appendix, no. 3

#### **B. Review of TSE Clearance Studies**

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One (1) Page Determined to be Non-Releasable: (b)(4)

The FDA questions (in bold) and the summarized CSLB responses (regular font) here are limited to the assigned CMC sections. The question numbers below follow the original numbering in the information requests sent to the firm. Reviewer comments are indicated in italics after CSLB’s responses.

**A. First Information Request (Sent on 5-NOV-09, Responses received on 30-NOV-09 and on 29-JAN-10)**

After initial review, an information request was sent to CSLB on 5-NOV-09. This review only covers responses to questions 14-23. Majority of the responses and attachments can be found in the BLA amendment STN 125350/0.5 (received on 30-NOV-09), except for the responses to the -----(b)(4)----- Diphtheria Antitoxin specification questions which can be found in BLA amendment STN 125350/0.13 (received on 29-JAN-10, see Section C below for these responses).

**14. The proposed specification for Appearance, “...*light brown solution* -----(b)(4)-----”, represents a reduction in product quality standards compared to the current IgPro10 specification. Please provide an appropriate justification for the lowering of this specification. Also, please provide additional information on the following related items:**

CSLB Response: The proposed specification for IgPro20 appearance was based on the -----(b)(4)----- on subcutaneous IgG which lists the following: “The liquid preparation is clear and pale-yellow or light brown; -----(b)(4)-----  
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*See follow-up review questions to the responses to Question 14 in Section B below (23-DEC-09 IR).*

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

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**16. Please specify the following “other characteristics/batch-related requirements”:**

**a. Visual inspection (100% of the bottles are controlled)**

CSLB Response: CSLB confirmed that IgPro20 undergoes 100% visual inspection (according to SOP P034000D, General Guidelines for Visual Inspection) after aseptic filling. All vials not in compliance with the set requirements are discarded. Specially trained and qualified analysts perform visual inspection ----- (b)(4) ----- . Different defect categories are noted, i.e., turbidity, flakes, foreign particles, glass defects, printing and crimp cap defects, stopper defects, and filling level. Each category has a defined action limit. If the number of discarded vials in a category exceeds the action limit, a deviation investigation is initiated.

**b. Date of manufacture**

CSLB Response: The date of manufacture is defined as the date of final sterile filtration.

**c. Transport conditions**

CSLB Response: The storage and transport conditions for the IgPro20 final product are 2-25 °C, protected from light.

17. When using Reference Immune Globulin Lot 176 (a 16.5% IgG solution) for purposes of meeting the minimum potency requirements for anti-measles and anti-polio type 1 in IgPro20 (a 20% IgG solution), the potency ratios should be adjusted to correct for the difference in IgG concentration. Thus, the adjusted minimum ratio for anti-measles for lot release of IgPro20 should be (b)(4)- if the required ratio for a 16.5% IgG solution is set at (b)(4)-. Please use the adjusted ratio in the lot release protocol.

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18. For diphtheria antitoxin, the specification listed in Table 3 (Batch analysis report, pg 8 of 10) is (b)(4)- ----- . Please use the US Standard Diphtheria Antitoxin for validation and express the specification for lot release as U (units)/mL. The minimum ratio for a 16.5% IgG solution is 2 units (U)/mL and hence the adjusted ratio for IgPro20 is close to --- (b)(4) --. Please provide the conversion ratio between IU and U.

CSLB Response: CSLB stated that the limit and unit of --- (b)(4) --- is in line with the currently licensed products, Privigen and Carimune NF. CSLB will determine and provide a conversion ratio between IU and U, as well as the method validation results expressed in US units/mL. CSLB said they would submit the information by the end of January 2010, which FDA allowed.

*CSLB submitted on 29-JAN-10 the revised validation report for testing diphtheria antitoxin in IgPro20 by --- (b)(4) --- method (see STN 125350/0.13 Amendment for the response).*

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21. You submitted method summaries and validation reports for the Parvovirus B19 NAT methods of the ----- (b)(4) -----, however, their intended uses were not specified.
- a. Please clarify which methods will be used to test B19 in:
- i. --- (b)(4) --- and manufacturing pools

CSLB Response: Manufacturing pools are tested for B19V DNA at the laboratories listed in Table 9 below. ----- (b)(4) -----

**Table 9:** Laboratories for B19V DNA testing on manufacturing pools

Laboratory	Intended Use
--(b)(4)---	Routine testing laboratory
-(b)(4)-	Back-up testing laboratory (first-line)
-(b)(4)-	Back-up testing laboratory (second-line)

- ii. Source Plasma and recovered plasma

CSLB Response: Source Plasma and recovered plasma are tested for B19V DNA at the following laboratories listed in Table 10 below:

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

- b. Please provide additional information regarding the testing sensitivities for --(b)(4)-- NAT screening and cut-off levels in terms of original plasma donations being excluded from manufacturing.

CSLB Response: Testing sensitivities for --- (b)(4) --- NAT screening and cut-off levels in terms of original plasma donations are listed below:

**Table 11:** Testing sensitivities for --(b)(4)-- NAT screening and cut-off levels

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

22. There are conflicting reports in your submission regarding your endotoxin test method and specification. In the Biological Requirements section, the method and specification are listed as

**Q000443D and ----(b)(4)----, respectively. Meanwhile, in the Characterization of Impurities section, the method and specification are listed as Q000081D and --- (b)(4)--- (if using -(b)(4)- test), respectively. Please clarify.**

CSLB Response: The endotoxin test methods (----- (b)(4) -----) described in Q000443D and Q000081D are identical, except that the readout is made on different equipment. The method described in Q000443D is used for release testing of the final product, for all in process controls as well as for routine testing of all raw materials. The upper limit of endotoxin in the final product is specified as --- (b)(4) ---.

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**23. For your anti-Polio Type 1 method validation, please tabulate the validation results (in IU/mL) side-by-side with the equivalent values in “x Ref 176 CBER” for easier comparison.**

CSLB Response: A new version of the anti-Polio Type 1 method validation report has been generated that includes the validation results in equivalence ratios to CBER Ref. Lot 176, indicated in brackets (see 3.2.P.5.3 Validation of Analytical Procedures Att. 13 VR Anti-Polio, Table 1). For instance, CSLB now lists the validated range as “----- (b)(4) ----- (equivalent to --- (b)(4) -- x Ref)”.

**B. Second Information Request (Sent on 23-DEC-09, Responses received on 15-JAN-10)**

This review contains CSLB’s responses to follow-up questions sent by FDA CBER on 23-DEC-09 after evaluating CSLB’s responses to the 5-NOV-09 IR (specifically, questions 5, 14, 14a, 14b, 14c, 15a, 18, 21). Also included below are CSLB’s responses to additional questions sent in the 23-DEC-09 IR regarding the Pyrogen Test, Identity Test, and -(b)(4)- NAT (see STN 125350/0.9 Amendment, received on 15-JAN-10).

**Re: Review of Responses to Questions 5, 14, 14b:**

**For the FDA-licensed subcutaneous immune globulin product, Vivaglobin, the specification for Appearance is listed as: “Clear solution. Color can vary from colorless to pale yellow”. --- (b)(4) ---**

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-----; therefore, we recommend that you adopt an Appearance specification for IgPro20 (at lot release) that is similar to that of Vivaglobin.

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*FDA CBER agrees to IgPro20 having two separate Appearance specifications (one for lot release and one for end-of-shelf-life. However, FDA CBER recommends limiting what constitutes “----- (b)(4) -----” in the Appearance specification (end-of-shelf-life) by specifying the ----- (b)(4) ----- . These should be based on the stability data of the IgPro20 lots used in the clinical trials.*

**Re: Review of Response to Question 14a:**

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**Re: Review of Response to Question 14c:**

- 1. Please provide the visual inspection results for the following US clinical trial lots after aseptic filling: lot numbers 43109-00001, 43109-00002, 43109-00003, 43109-00004, 43109-00005, and 43109-00006.**

CSLB Response: The results of the US clinical trial lots 43109-00001, 43109-00002, 43109-00003, 43109-00004, 43109-00005, and 43109-00006 are summarized in Attachment 01. (These results have also been included in Attachment 5 of CSLB’s 30-NOV-09 response letter, however, with reference only to the filling lot numbers.)

- 2. Have these lots been placed on stability monitoring as well? If so, please provide the stability results to date. We also request that you provide a more detailed description of the stability results beyond the usual “pass/fail” for these lots, i.e., for quantitative assays, the numerical value of the test result.**

CSLB Response: The table below summarizes the date of manufacture of lots 43109-00001, 43109-00002, 43109-00003, 43109-00004, 43109-00005, and 43109-00006 and listing which ones have been placed on stability monitoring. Attachments 02 and 03 contain the stability reports including more detailed descriptions of the results.

Table 12: US Clinical Lots on Stability			
Packing Lot	Filling Lot	Stability Study No.	Date of Manufacture
43109-00001	05943-00002	RSTAB0049	28-FEB-06



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

CSLB Response: The ---(b)(4)--- size used for B19V NAT testing at -----(b)(4)-----.

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

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c. **Clarification of the cut-off level of -----(b)(4)----- B19 DNA for the single donation versus the testing sensitivity of -----(b)(4)----- for the single donation listed in Table 9 (CSLB response letter dated 5-NOV-09). Please provide the procedure, e.g., -----(b)(4)-----, for approaching such a cut-off level when a qualitative NAT procedure is used.**

CSLB Response: The -----(b)(4)--- assay used by ---(b)(4)--- for --(b)(4)-- testing is a qualitative assay with an assay sensitivity of -----(b)(4)----- and a sensitivity relating to the single donation of -----(b)(4)----- that test positive (i.e. contain  $\geq 1000$  IU/mL B19V DNA) are resolved, and the implicated B19V-positive donations are discarded. The current quality requirements for B19V --(b)(4)--- NAT testing define a cut-off level of -----(b)(4)----- B19 DNA. Please note this relates to and is aligned with the process requirement of  $<10^4$  IU/mL at the manufacturing pool level. Therefore, the cut-off applied for B19V minipool NAT testing performed by ----(b)(4)--- is more stringent than that defined by the quality requirement.

d. **The resolution time between Whole Blood collection and identification of single B19 DNA-positive donation(s). Please shorten such resolution time so that a meaningful notification or retrieval is feasible within the dating period of any cellular blood component associated with high-titer donations that will be excluded from manufacturing.**

CSLB Response: Days to months may pass from collection before a blood center decides to designate plasma as recovered plasma to sell to a fractionator versus selling it as FFP to a hospital. Therefore the decision to test for B19 DNA is necessarily delayed. CSLB's goal in working with ----(b)(4)--- lab is to test the plasma that blood centers have designated to be purchased by CSLB. Typically test results are reported by ---(b)(4)-- to CSLB within two weeks and on occasion much longer. CSLB has no direct control over the blood banks' decisions about who they sell their plasma components to.

e. **A summary description of -----(b)(4)----- B19 NAT method with details on the sample preparation, sample input volume, sequences and map locations of the primers and probes used, and cycling conditions. Please also provide a copy of -----(b)(4)----- SOP for B19 NAT.**

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The information regarding sequences and map locations of primers and probes is proprietary information owned by ---(b)(4)---. This information will be provided directly by ----(b)(4)--- according to the letter of

access (Attachment 05). For ----(b)(4)----- SOPs and forms for B19V NAT testing please refer to Attachment 06 bundle.

*During the 4-FEB-10 teleconference, CSLB informed FDA CBER that ---(b)(4)--- submitted the information regarding the sequences and map locations of their B19 NAT primers and probes. In addition, CSLB said that ----(b)(4)---- B19 NAT assay is a validated in-house method, however, it is not licensed, therefore has no assigned Drug Master File number.*

**f. -(b)(4)- analysis of all their B19-specific primers and probes to demonstrate that all three known genotypes can be efficiently detected.**

CSLB Response: The -(b)(4)- analysis data of all their B19-specific primers and probes is proprietary information owned by ---(b)(4)--. This information will be provided directly by ---(b)(4)--- according to the letter of access (Attachment 05). CSLB agrees to provide the following information from -----

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

-----:

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

**g. Validation of ----(b)(4)---- B19 NAT method done according to the ICH and OMCL guidelines. Please provide copies of the method validation protocol and the validation study report.**

CSLB Response: A copy of the combined method validation protocol and validation study report is in Attachment 07 (VP09.004).

**h. Prevalence of high-titer, B19 DNA-positive recovered plasma donations since the implementation of such minipool screening.**

CSLB Response: CSLB does not track epidemiology for this analyte as all recovered plasma used in this product is tested for B19V by blood center labs. However, according to ---(b)(4)----, the prevalence of B19V DNA positive recovered plasma donations since the implementation of B19V NAT testing at ---(b)(4)-- is -(b)(4)- donations (39 B19V-positive donations out of -(b)(4)- samples tested since August 2009).

**2. Since BSL's ---(b)(4)-- NAT procedure is a qualitative test, please also clarify how you approach the cut-off level of -----(b)(4)----- for the single donation when the testing sensitivity for the single donation is -----(b)(4)----- of B19 DNA (listed in Table 9).**

CSLB Response: The B19V NAT assay used by -(b)(4)- for -(b)(4)- testing is a qualitative assay with an assay sensitivity of ----(b)(4)--- (95% cut-off) and a sensitivity relating to the single donation of --(b)(4)--- ----- that test positive (i.e. contain ----(b)(4)---- B19V DNA) are resolved, and the implicated B19V-positive donations are discarded. The current quality requirements for B19V ---(b)(4)-- NAT testing define a cut-off level of -----(b)(4)----- B19 DNA. Therefore, the cut-off applied for B19V ---(b)(4)-- NAT testing performed by -(b)(4)- is more stringent than that defined by the quality requirement.

**3. Please provide a description and the relevant SOPs for the receipt, tracking, and management of B19 --(b)(4)-- NAT results received from ----(b)(4)----. Please also provide the procedures for the quarantine and disposal of high-titer B19-positive recovered plasma donations.**

CSLB Response: The plasma is quarantined at CSL Plasma as long as B19 NAT test results are pending. Test results for B19V NAT from ---(b)(4)--- are received as electronic files by CSLB AG and are uploaded into the system for plasma identification (SPI). In SPI, units that are unsuitable are flagged by a discrepancy in the system. Once all units of a certain shipment have received all results, the shipment may be delivered to

the fractionator. At the fractionator site, all the units in every shipment are scanned to identify unsuitable units that are flagged by discrepancies (100% unit verification). After automated removal of all discrepant units, including those with positive test results, into a separate bin the plasma is allocated to a plasma pool and may be manufactured. A print out from SPI of all discrepant removed units is made and is used to countercheck that all removed units have been separated physically from the manufacturing pool. The bin with the removed units is then forwarded to the logistics group, which is responsible to initiate the external destruction of the units. Destruction of the units by the external contractor is confirmed to the logistics group.

For SOPs relevant for the receipt, tracking and management of B19V NAT --- (b)(4) -- results received from --- (b)(4) --- please refer to the Attachment 08 bundle.

**Re: Samples Needed for Conformance Lot Testing:**

**Please contact CBER Product Release Branch and provide the following samples for conformance lot testing as soon as possible:**

- 6 vials of each 5 mL fill lot (lots ----- (b)(4) -----);**
- 3 vials of each 20 mL fill lot (lots ----- (b)(4) -----).**

**Please identify that the shipment and vials are in support of STN 125350, and contact Ms. Rana (RPM) when you have shipped these vials.**

CSLB Response: CSLB agreed to submit the above stated number of vials of conformance lots to the CBER Product Release Branch, and Ms. Rana, the RPM, will be notified at the time of shipment of these vials.

**Re: Samples Required for Routine Lot Release Testing**

**Please contact CBER Product Release Branch and provide 6 vials of 5 mL fill lots, 4 vials of 10 ml fill lots, 3 vials of - (b)(4) - fill lots, and 2 vials of 20 mL fill lots for CBER lot release testing. Please identify that the shipment and vials are in support of STN 125350. Please contact Ms. Rana (RPM) when you have shipped the requested vials.**

CSLB Response: CSLB agreed to submit the above stated number of vials for routine lot release to the CBER Product Release Branch. Ms Rana, the RPM, will be notified at the time of shipment of these vials. Please note that the lots have not been manufactured yet but will be manufactured later this year.

**Re: Pyrogen Test**

**Please note that the testing of all lots of final drug product must include a test done in rabbits for pyrogenic substances, as required by the United States Code of Federal Regulations, Title 21, Part 610.13(b). This requirement is mandatory, and may not be waived. However, under 21 CFR 610.9, an application may be made for the use of an equivalent method that provides equal or greater assurance of safety and purity of the product. Such an application should include rabbit pyrogen test results, compared to test results by the proposed equivalent method, for a number of final product lots sufficient to robustly demonstrate 1) equivalent or better test accuracy and precision; and 2) ongoing consistency and adequate control of facility environment and production bioburden levels.**

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*FDA CBER finds CSLB’s comparability study to be insufficient. While the submitted data shows consistently low levels of pyrogens in rabbits and of -----(b)(4)----- test method, these do not demonstrate whether a IgPro20 lot with enough pyrogens to fail the RPT would also be failed by the -(b)(4)- test. As a condition of approval, FDA CBER requires CSLB to perform the RPT on the final product lots of IgPro20. If CSLB still wishes to change test methods, FDA CBER suggests performing comparability studies between the two tests by analyzing IgPro20 samples that have been -----(b)(4)----- to determine how well the two methods correlate.*

**Re: Identity Test**  
**Please note that you may eliminate the reporting of the Identity Test result from the Lot Release Protocol of IgPro20; i.e., remove item no. 4: “Identity: Performed after packing”.**

CSLB Response: CSLB takes note of the agreement of the agency.

**Additional Information Request: Review of -(b)(4)- NAT**

**In your submission, in addition to in-process B19 NAT testing, -(b)(4)- NAT testing has likewise been**

implemented. Please submit the relevant information (see below) regarding your in-process (b)(4)- NAT testing.

(b)(4)

1. (b)(4)- NAT procedures for testing Source Plasma and recovered plasma donations. For each method, please provide the following information:

CSLB Response: Source Plasma donations are NAT-tested in (b)(4)- for (b)(4)- using the (b)(4)- assay. Recovered plasma donations are not tested for (b)(4)-.

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**C. Responses to Remaining Items from 5-NOV-09 and 23-DEC-09 IR (Received on 29-JAN-10)**

This response package (STN 125350/0.13 Amendment) contains information that completes the responses to the 5-NOV-09 IR questions 15a and 18, that were also mentioned in the 23-DEC-09 IR.

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**2. Review of Response to Question no. 18: You may submit data to support the conversion ratio between international units (IU) and the U.S. units (U) as well as the method validation results expressed in U/mL for diphtheria antitoxin testing on IgPro20 final product before the end of January 2010.**

CSLB Response: CSLB’s in-house standard (b)(4)- was calibrated against the U.S. standard diphtheria antitoxin for neutralization (F4508). This same (b)(4)- standard was calibrated against the WHO diphtheria antitoxin standard. The conversion factor resulting from these calibrations is 1.0 IU/mL = 1.0 (U.S.) U/mL. The table and graph below show the individual values obtained in the two calibrations. A new version of the validation report has been composed, which states that WHO and CBER units are equivalent. Results obtained in IU/mL are therefore interchangeable with results in U/mL in this diphtheria ----- (b)(4) ----- test.

[  
--(b)(4)--  
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The method validation results are now expressed in U/mL for diphtheria antitoxin testing on the IgPro20 final product in 3.2.P.5.3 Att. 16 VR Diphtheria Antitoxin.

*This updated version now includes the conversion factor between the WHO and US units, which is 1.0 IU/mL = 1.0 U/mL (see Section 7.3 Reference Material in 05002.12. -(b)(4)-.012\_02, Attachment 16 in STN 125350/0.13). It also states that all values shown in IU/mL are equivalent to values in U/mL.*

## **APPENDIX**

### **Supporting documents submitted in the Original BLA submission (STN 125350/0) that were reviewed in this memo:**

#### **1. Product Specifications, Analytical Procedures, Validations of Analytical Procedures**

- a. 3.2.P.5.1 Specifications – contains tables of proposed specifications for IgPro20 final product classified according to physicochemical, biological and immunological requirements; additional stability tests
- b. 3.2.P.5.2 Analytical Procedures – contains a table with brief descriptions of all the analytical methods used for testing the final product
- 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: -----(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: -----(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)----- Assay)(approved 1-DEC-08)(section 3.2.P.5.3, Attachment 09)

- mm. 05002.12.-(b)(4)-.023\_01 Validation Report for Analytical Method: Bacterial Endotoxins Test  
-(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\_01 Validation Report for Analytical Method: Anti-Polio Antibodies (approved 30-APR-08)(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 immunoglobulin liquid  
(approved 6-MAR-09)(section 3.2.P.5.3, Attachment 24)

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

- a. Analytical Procedure Summary B19 --- (b)(4)-- Method (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)----- (performed at --(b)(4)--)  
(approved 9-APR-08)(section 3.2.S.2.3, Attachment 08)
- c. Analytical Procedure Summary B19 -(b)(4)- Method (plasma pools) ----- (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 fraction -(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)

**Supporting documents submitted in the 5-NOV-09 IR Response Package (STN 125350/0.5, received 30-NOV-09) that were reviewed in this memo:**

- a. -----(b)(4)-----  
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- b. -----(b)(4)-----  
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- c. -----(b)(4)-----  
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- d. Review Article: Chouskey, A., Duff, K., Wasserbauer, Berger, M. 2005. Subcutaneous immunoglobulin-G replacement therapy with preparations currently available in the United States for intravenous or intramuscular use: reasons and regimens. Allerg. Asthma. Clin. Immunol. 1 (3): 120-130 (Quality, Attachment 08)
- e. BB-IND -(b)(4)-, Serial No. 045: Rationale that -----(b)(4)----- Testing Does Not Apply to IGSCs (dated 16-JAN-09)(Quality, Attachment 09)
- f. 05002.12.-(b)(4)-.011\_02 Validation Report for Analytical Method: Anti-Polio Antibodies (approved 13-NOV-09)(section 3.2.P.5.3, Attachment 13) – *inclusion of results in units (x CBER Ref. Lot 176)*

**Supporting documents submitted in the 23-DEC-09 IR Response Package (STN 125350/0.9, received 15-JAN-10) that were reviewed in this memo:**

- a. IgPro20: Results of the Visual Inspection (Quality, Attachment 01) – *6 clinical lots visually inspected between 1-MAR-06 to 9-NOV-07.*
- b. RSTAB0049F3601\_01\_5°C: --(b)(4)-- Final Stability Study Report, Long-Term Conditions (--(b)(4)-- at 5 °C), Two Clinical Lots IgPro20, -(b)(4)-, stored at 5 °C (approved 12-JAN-10)(Quality, Attachment 02) – *Stability data of 2 clinical lots, 05943-00002 and 05943-00003, stored at 5 °C up to --(b)(4)--.*
- c. RSTAB0049F3601\_01\_25°C: --(b)(4)-- Final Stability Study Report, Long-Term Conditions (--(b)(4)---- at 25 °C), Two Clinical Lots IgPro20 stored at 25 °C (approved 12-JAN-10) (Quality, Attachment 03) – *Stability results for the 2 clinical lots, 05943-00002 and 05943-00003, stored at 25 °C up to -(b)(4)-.*
- d. --(b)(4)---- Parvo B19 Virus Pooled Testing Diagram (-(b)(4)- 7/09 version)(Quality, Attachment 04) – *from Master Pool of -(b)(4)- samples*
- e. Letter of Authorization from ----(b)(4)--- to FDA CBER (dated 7-JAN-10 from -----(b)(6)-----, Chief Science Officer, ---(b)(4)-- Testing Laboratory) (Quality, Attachment 05) – *Letter authorizes FDA to*

*make reference to the primer and probe sequences, mapping and -(b)(4)- analysis data of their Human Parvo B19 virus Assay*

- f. ---(b)(4)--- SOP 04.1100 Preparing Samples for B19 (Doc. No. LS-02427, revision 4)( (Quality, Attachment 06)
- g. ---(b)(4)--- SOP 04.1101 Preparation of Parvovirus B19 Assay Reagents (Doc. No. LS-02504, revision 0)( (Quality, Attachment 06)
- h. ---(b)(4)--- SOP 04.1102 Operation and Maintenance of the ------(b)(4)----- (Doc. No. LS-02509, revision 1)( (Quality, Attachment 06)
- i. ---(b)(4)--- SOP 04.1103 Operation of -----(b)(4)----- Instrument (Doc. No. LS-02512, revision 0)( (Quality, Attachment 06)
- j. ---(b)(4)--- SOP 04.1104 Review of Parvovirus B19 Assay Test Results (Doc. No. LS-02513, revision 1)( (Quality, Attachment 06)
- k. ---(b)(4)--- SOP 04.1105 Reporting Parvovirus B19 Assay Results (Doc. No. LS-02516, revision 1)(Quality, Attachment 06)
- l. ---(b)(4)--- Validation Plan for Qualitative NAT Testing for Parvovirus B19 DNA (approved 17-APR-09, effective 4-AUG-09) (Quality, Attachment 07)
- m. CSL Plasma SOP No. POP8021: Daily Receipt of Test Results (Version 16, effective 20-AUG-09)(Quality, Attachment 08) – *covers results from -(b)(4)- Testing for viral markers*
- n. CSL Plasma SOP No. POP8031: Unsuitable Events Management (Version 18, effective 27-JUL-09)(Quality, Attachment 08)
- o. CSL Plasma SOP No. POP8041: Unacceptable Test Results Flow Log (Version 15, effective 20-AUG-09)(Quality, Attachment 08)
- p. CSL Plasma SOP No. POP8091: Manual Quarantine Process (Version 1, effective 20-AUG-09) (Quality, Attachment 08)
- q. CSL Plasma SOP No. POP9011: Managing Plasma Unit Inventory (Version 6, effective 23-NOV-09) (Quality, Attachment 08)
- r. CSL Plasma SOP No. POP9032: Reviewing Records for Shipment Release (Version 4, effective 20-AUG-09) (Quality, Attachment 08)
- s. ------(b)(4)----- (512) (Quality, Attachment 09)
- t. Letter of Authorization to Reference ------(b)(4)----- Master File BB/MF -----(b)(4)---- (dated 6-JAN-10 from -----(b)(6)----- of Regulatory Affairs/Quality Assurance) - Letter authorizes FDA to reference -(b)(4)- Master ------(b)(4)----- Assay (Quality, Attachment 10).
- u. ------(b)(4)----- Assay Flow Chart (Quality, Attachment 11).
- v. Validation Summary of the ------(b)(4)----- Assay (Quality, Attachment 12)
- w. Validation Summary of the ------(b)(4)----- Assay (Quality, Attachment 13)
- x. -(b)(4)- STDY 226 and Addendum 1: Determination of the Analytical Sensitivity of the ------(b)(4)----- Assay Utilizing the -----(b)(4)--- International Standard. (approved 4-MAY-06) (Quality, Attachment 13, Sub-Attachment 1)
- y. -(b)(4)- Validation Report PV 152: Demonstration of the Robustness of the ------(b)(4)----- Assay (approved 15-FEB-02) (Quality, Attachment 13, Sub-Attachment 2)
- z. -(b)(4)- Validation Report PV 146: Demonstration of Specificity for the ------(b)(4)----- Assay (approved 27-NOV-01) (Quality, Attachment 13, Sub-Attachment 3)

**Supporting documents submitted in the “Remaining” IR Response Package (STN 125350/0.13, received 29-JAN-10) that were reviewed in this memo:**

- a. SOP Q000482D\_01: Octanoic acid in immunoglobulins (version 01, valid 27-JAN-10) (section 3.2.P.5.2, Attachment 27)
- b. 05002.12. -(b)(4)-.012\_02 Validation Report for Analytical Method: Diphtheria Antitoxin (version 2, approved 25-JAN-10)(section 3.2.P.5.3, Attachment 16)
- c. 05002.12. -(b)(4)-.044\_01 Validation Report for Analytical Method: -----(b)(4)----- (approved 21-JAN-10)(section 3.2.P.5.3, Attachment 25)