



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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MEMORANDUM

Date: September 13, 2016

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Subject: Final Product Review Memo  
Product: Immune Globulin Subcutaneous (Human), 20% Solution  
Date: September 14, 2015  
Sponsor: Baxalta

**Executive Summary:**

Approval is recommended. There are no follow-up issues from the product review standpoint.

The Sponsor's IGSC, 20% product is manufactured (b) (4) [REDACTED]. Process validation for the new manufacturing steps appears adequate. A small number of conformance and clinical batches were manufactured by the Sponsor, in separate campaigns, using routine (b) (4) intermediate manufactured using the licensed process. There were small differences in the final manufacturing steps used in the clinical and conformance lot campaigns. Nevertheless, the conformance and clinical final product batches were highly similar to each other. Manufacturing deviations (sterile filter reduced flow rate) associated with the conformance lot campaign were addressed in a pre-BLA meeting. Investigations and CAPAs were deemed adequate at that time. Clinical and conformance lots met all release specifications. Extended analysis included (b) (4) [REDACTED] assessment, which was inadequate and requires follow-up. As expected, IGSC 20% has a slightly worse stability profile than IGI, 10%. The stability data presented are supportive of the Sponsor's proposed storage conditions and shelf life.

**Review:**

In this electronic BLA submission the Sponsor introduces Cuvitru, an IGSC, 20% preparation highly similar to the Sponsor's approved Gammagard Liquid IGI, 10% product. The IGSC, 20% product differs in the (b) (4) and formulation steps, and is intended for subcutaneous route of administration only. The manufacturing process from starting plasma through (b) (4).

**Manufacturing Overview: Drug Substance****Manufacturing of IGSC, 20% (b) (4)**

For manufacturing IGSC, 20% the Sponsor utilizes a modified Cohn-Oncley cold ethanol fractionation procedure to isolate an intermediate fraction called (b) (4) from (b) (4) human plasma. Fractionation of starting plasma and (b) (4) production occurs in the Sponsor's currently licensed facilities in (b) (4). (b) (4) batches from the three facilities are shipped (b) (4) to the Sponsor's facility in (b) (4) for further processing. Immune globulin is isolated from (b) (4) by cation and anion exchange chromatography. Pathogen inactivation and removal are effected by three dedicated steps: solvent/detergent treatment, nanofiltration, and low pH / elevated temperature hold (b) (4). A (b) (4) glycine buffer (b) (4) achieves the desired formulation criteria of pH 4.6-5.1 and a concentration of huIgG between (b) (4).

**Validation of Upstream Manufacturing Steps in IGSC, 20% Process**

Essentially all data presented to support upstream manufacturing steps in IGSC 20% were previously submitted to support the Sponsor's IGI, 10% BLA. Importantly:

- 1) Critical process controls and study reports justifying limits including virus inactivation by S/D and nanofiltration parameters were submitted, reviewed, and approved as part of IGI, 10% licensure.
- 2) Characterization of impurities and analysis of purification steps which remove impurities were all submitted previously to the IGI, 10% BLA.
- 3) Data supporting comparability of (b) (4) batches prepared at (b) (4), and (b) (4) facilities were submitted to the IGI, 10% BLA.
- 4) Validation studies of analytical methods was similarly submitted and approved previously.

The Sponsor does note that (b) (4)

(b) (4) entering the IGSC, 20% manufacturing stream will only be (b) (4). Routine (b) (4) representing (b) (4) were included in the Sponsor's process validation studies noted below.

**Information Provided on Drug Product Manufacture: General**

The drug product is a purified 20% IgG isotonic solution, containing approximately 200 mg protein per mL of which at least 98% is IgG, with a pH of 4.6 to 5.1 and glycine stabilizing agent at (b) (4). Composition of the biologic product is shown in Table 1, below.

**Table 1. Target Composition of IGSC, 20%**

Name of Component	Unit and/or Percentage Formula				Function	Reference to Standard
Protein (with at least 98% IgG)	1 g/vial	2 g/vial	4 g/vial	8 g/vial	Active ingredient	(b) (4)
	<b>Other Ingredients</b>					
Glycine	(b) (4)				Stabilizing agent	
Water for injection to a final volume of:	5 mL	10 mL	20 mL	40 mL	Drug carrier	

The Sponsor notes that (b) (4) batches are generated from (b) (4) of plasma. At (b) (4), (b) (4) batches are combined to process final container batches that represent (b) (4) of starting plasma.

**Table 2. Approximate Batch Size of IGSC, 20%**

(b) (4)

**Information Provided on Drug Product Manufacture: Process Validation**

Appropriate in-process controls related to the final manufacturing steps as follows (Table 4, below). The in-process controls include a (b) (4). (b) (4)

. Validation of the proposed (b) (4) was performed successfully at (b) (4) in study IGSC\_1-SD-11-B-SR (April 7, 2015).

**Table 3: In Process Controls, Downstream Manufacture IGSC, 20%**

(b) (4)

**Conformance Lot Manufacture:** The Sponsor notes that upstream steps were previously validated in studies submitted and reviewed to support Gammagard Liquid. Therefore the Sponsor used routine (b) (4) lots as the starting manufacturing point for its validation studies of IGSC, 20%. The validation study encompassed (b) (4) batches prepared by (b) (4)

. Summary batch information for the conformance lots is provided in Table 5. The Sponsor notes that the six clinical study lots of IGSC, 20% (LE13H001, LE13K001, LE13N001, LE14N003, LE13P002) were prepared in a separate manufacturing campaign, and manufacture included a sterilizing filtration (b) (4)

(b) (4). See Figure 1 below.

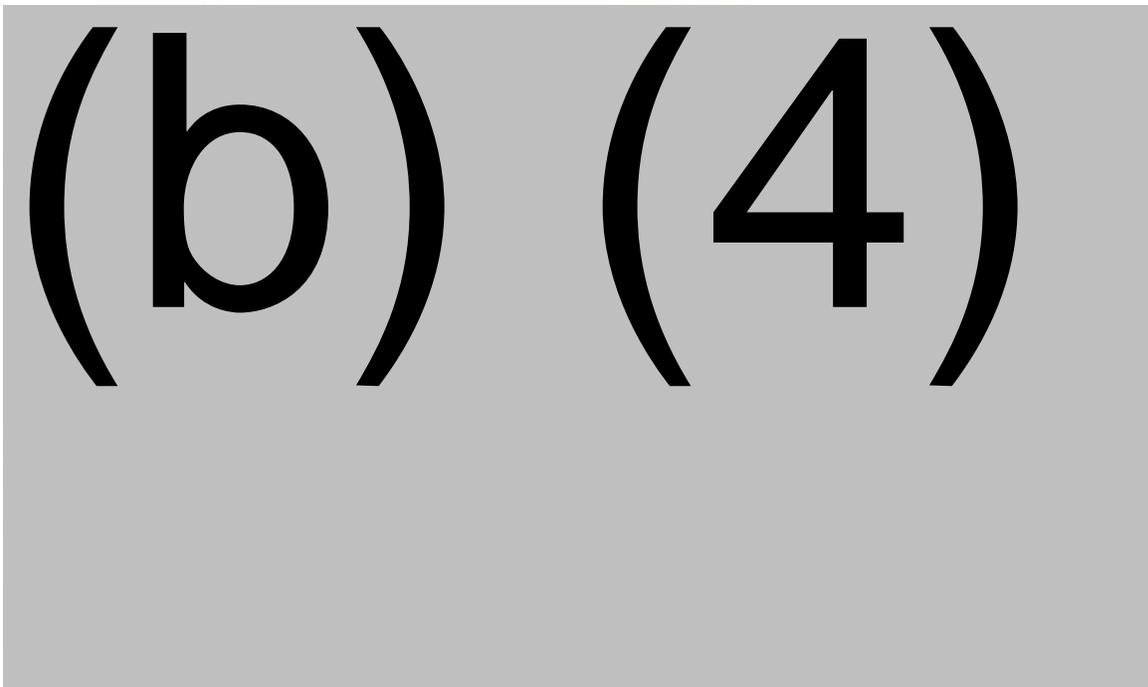
The differences between clinical and conformance batch manufacture were discussed with FDA in a type C meeting in November 2014. FDA agreed that these differences would not confound the interpretation of the clinical study. Deviations encountered during preparation of the conformance batches included a lower than target final protein concentration and reduced flow rate during sterile filtration (called “clogging” in the actual study) (b) (4)

. Investigations and corrective actions associated with these deviations were reviewed and found acceptable by FDA in November 2014.

**Table 4: Information on IGSC, 20% Conformance Study Lots**



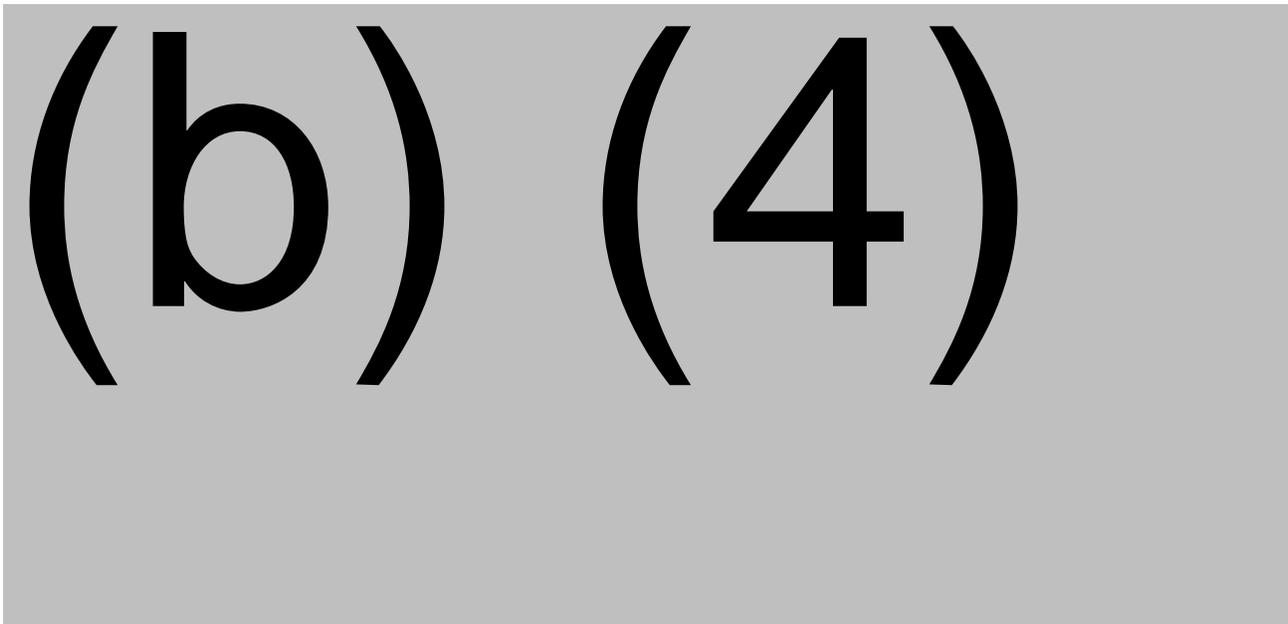
**Figure 1: Comparison of Clinical vs Conformance Batch Manufacture**



*Study VP-TS-DIV-15-001 (March 6, 2015)* details the comparability assessment of IGSC, 20% final container lots. No differences were observed in product characteristics such as (b) (4) [redacted], total protein, identity or purity. Contaminants such as residual solvent and

detergent were similarly very low in all batches. Titers of specific antibodies were not different across all (b)(4) batches of IGSC, 20% (Figure 2, below).

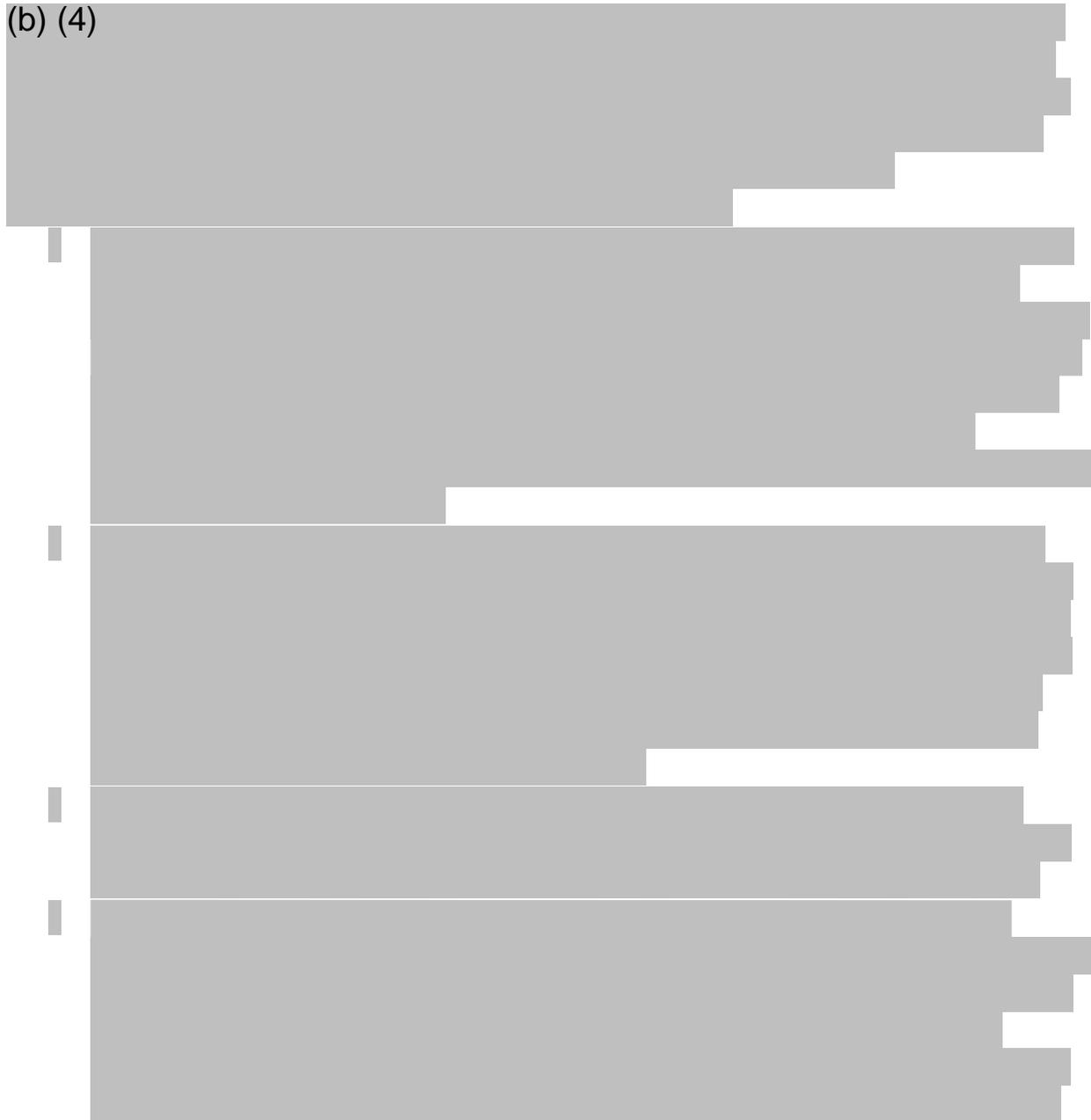
**Figure 2: Comparison of Clinical and Conformance IGSC 20% Lots**



**Figure 3 : (b) (4) Analysis in IGSC 20% Lots**



(b) (4)



**Release Specifications:**

Appearance: Product has “light-brown” added as an allowable visual inspection characteristic, based on the Sponsor’s evaluation of the clinical lots. There is no mention if the conformance lots were “light-brown”. This is different from the description of IGI, 10%. Yellow-brown was an approved characteristic for Hizentra (CSLB 20% IGSC).

Doubling of Most Other Specifications: Limits both for antibody specificities and for undesirable contaminants (IgA, (b) (4), residual S/D) are (b) (4) the specification for the 10% product. Exceptions are sterility, (b) (4), identity, protein identity, purity, glycine, pH, and bacterial endotoxin (b) (4).

Stability Properties: Clinical versus conformance lots, 25°C (b) (4). In each graph, clinical lots are shown in blue and conformance lots are in black. Stability data the Sponsor collected at 5°C demonstrated no change in stability indicating parameters. Data collected at 25°C (b) (4) are shown. Clinical and conformance lots demonstrated similar stability profiles, with trend toward worse stability at (b) (4) as expected.

(b) (4)

Overall the data suggest that the clinical lots and the conformance lots have similar stability properties despite the fact they were manufactured in separate campaigns. Separately, stability data for IGI, 10% and IGSC, 20% data were compared. As expected, the higher concentration product demonstrated worse stability parameters. However the parameters we analyzed at 25°C remained well within specification. Representative data comparing 10% and 20% product are shown at left.

(b) (4)

(b) (4)

Potency measures appeared similar between clinical and conformance IGSC, 20% lots. As expected, (b) (4) over time was faster (b) (4) than at 25°C.

Stability Conclusions: The increased concentration in the IGSC, 20% product results in a minor change in visual appearance upon reconstitution. (b) (4)

. The stability data together adequately support the Sponsor's proposed storage:

36 months from the date of manufacture when stored at 5°C.

12 months from the date of manufacture when stored at 25°C (b) (4) .

The Sponsor notes its intention to revise the shelf life at 25oC as additional data are collected.

