

## DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

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**To:** Administrative File STN 125596/0

**From:** Anthony Lorenzo, CSO, OCBQ/DMPQ/MRB II

**Through:** John A. Eltermann, Division Director, CBER/OCBQ/DMPQ  
Qiao Bobo, Branch Chief, OCBQ/DMPQ/MRB II

**Subject:** Baxalta USA Inc. (Baxalta) Biologics License Application 125596  
Immune Globulin Subcutaneous (Human), 20% Solution Original  
Biologics License Application

**Action Due:** August 14, 2016

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### RECOMMENDATION

Approval

### PRODUCT

Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%)

### REVIEW SUMMARY

IGSC, 20% is indicated by the subcutaneous route of administration for the treatment of primary immune deficiency disorders associated with defects in humoral immunity. These defects in humoral immunity include but are not limited to congenital X-linked agammaglobulinemia, common variable immune deficiency, Wiskott-Aldrich syndrome, and severe combined immune deficiencies.

Baxalta US Inc. (Baxalta) is currently licensed for the manufacture of Immune Globulin Infusion, (Human), 10% [IGI, 10%, under STN 125105]. The manufacturing process for IGSC, 20% utilizes almost identical manufacturing process steps as the currently licensed IGI with the exception of the (b) (4) and formulation steps. In addition, the concentration of IGSC is 20% rather than 10% and the route of administration is only subcutaneous.

The Baxalta manufacturing facilities involved in the production of IGSC, 20% are multi-product FDA licensed facilities. The fractionation lines and equipment in Baxalta's (b) (4),

(b) (4) facilities are shared for the manufacture of several plasma-derived-products. (b) (4) Baxalta’s (b) (4) facility is used for the purification of (b) (4) to IGSC, 20% and other immunoglobulin products. Final labeling and packaging of IGSC, 20% is also performed at the (b) (4) facility. The list of the Baxalta facilities used to manufacture IGSC, 20% is as follows:

Facility Address	Manufacturing Steps	FEI Number
(b) (4)	<ul style="list-style-type: none"> <li>• Fractionation of the pooled plasma to obtain (b) (4)</li> <li>• (b) (4) Testing</li> <li>• (b) (4) Stability Testing</li> </ul>	(b) (4)
(b) (4)	<ul style="list-style-type: none"> <li>• Storage of raw materials</li> <li>• Storage of intermediates, Final Drug Product, and released goods.</li> <li>• QA Receiving/Inspection sampling area.</li> <li>• Intermediates and Final Drug Product Shipping</li> </ul>	(b) (4)
(b) (4)	<ul style="list-style-type: none"> <li>• Fractionation of the pooled plasma to obtain (b) (4)</li> </ul>	(b) (4)
(b) (4)	<ul style="list-style-type: none"> <li>• (b) (4) Testing</li> <li>• (b) (4) Stability Testing</li> </ul>	(b) (4)
(b) (4)	<ul style="list-style-type: none"> <li>• (b) (4) Stability Testing</li> </ul>	(b) (4)
(b) (4)	<ul style="list-style-type: none"> <li>• Fractionation of the pooled plasma to obtain (b) (4)</li> <li>• (b) (4) Testing</li> <li>• (b) (4) Stability Testing</li> </ul>	(b) (4)
(b) (4)	<ul style="list-style-type: none"> <li>• Further manufacture of (b) (4) into IGSC, 20% Final Product</li> <li>• Final Product Testing and Release</li> <li>• Final Product Stability Testing</li> </ul>	(b) (4)

**NARRATIVE REVIEW**

**I. Environmental Analysis**

Categorical exclusion for the environmental analysis was requested according to 21 CFR 25.31(c). It is Baxalta’s position that IGSC, 20% naturally occurs in the environment. The approval of this BLA will not significantly alter the concentration or distribution of the IGSC, 20%, its metabolites or degradation products in the environment. To Baxter’s knowledge, no extraordinary circumstances exist as IGSC, 20% is a human plasma derived, highly purified, viral inactivated and sterile protein solution stabilized with 0.25 M glycine.

**Reviewer Comments:** The categorical exclusion has been submitted under 21 CFR § 25.31(c). The applicant states that to the applicant’s knowledge, no extraordinary circumstances exist. Approval of this naturally occurring product is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The categorical exclusion claim is accepted.

**II. Container Closure System**

The primary packaging components for the final product consists of a (b) (4) glass vial, a rubber stopper and an aluminum crimp cap. The sizes of the primary (b) (4) glass containers include 6 mL, 10 mL, 20 mL and 50 mL for product fill sizes 1 g, 2 g, 4 g and 8 g, respectively. The 6mL ((b) (4)) vial is a new vial size specific for IGSC, 20%. The other vial size formats are already in use at the facility for other licensed products. The type of stoppers and caps used for IGSC, 20% are identical and have the same dimensional specifications as the current stoppers and caps used for IGI, 10%. A (b) (4) test and (b) (4) test were performed to qualify the closure system of the new type of vial (b) (4).

**A. (b) (4) Test**

A (b) (4) test was performed as a feasibility study for the (b) (4) test. The test was carried out under protocol IGSC\_1-SD-20-C, “Container Closure System for Primary Packaging: Container Closure Integrity – (b) (4) Test.” The (b) (4) Test is based (b) (4)

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**Reviewer Comments:** Based on the satisfactory results, the container closure system consisting of the 20 mm stoppers, the glass vial (b) (4), and the aluminum caps bracketed by the maximum and minimum crimp pressure is validated as an effective microbial barrier.

### III. Manufacturing Process

#### A. Drug Substance Manufacturing

The IGSC, 20% drug substance manufacturing process employs a modified Cohn-Oncley cold alcohol fractionation procedure to isolate an intermediate IgG fraction, referred to as (b) (4), (b) (4) human plasma pools. Prior to cold ethanol fractionation, (b) (4)

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(b) (4)

**B. Drug Product Manufacturing**

**1. Process Steps**

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

(b) (4)

**b. Step (b) (4) - Sterile Filtration**

(b) (4)

(b) (4)



(b) (4)

(b) (4)

**c. Step (b) (4) - Aseptic Filling**

The sterile bulk solution is aseptically dispensed into final containers, stoppered and sealed under aseptic conditions and capped. Representative samples of the lot are removed and tested. The bulk solution can be filled at four different volumes, i.e., 5 mL, 10 mL, 20 mL, or 40 mL solution. Filling of several sub-lots (fill-sizes) from one bulk solution lot includes the following steps:

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

**d. Step (b) (4) - Low pH Incubation**

The filled vials are incubated at 30°C to 32°C for (b) (4) . Representative samples of the lot are removed and tested. The pH of the product after incubation is (b) (4) .

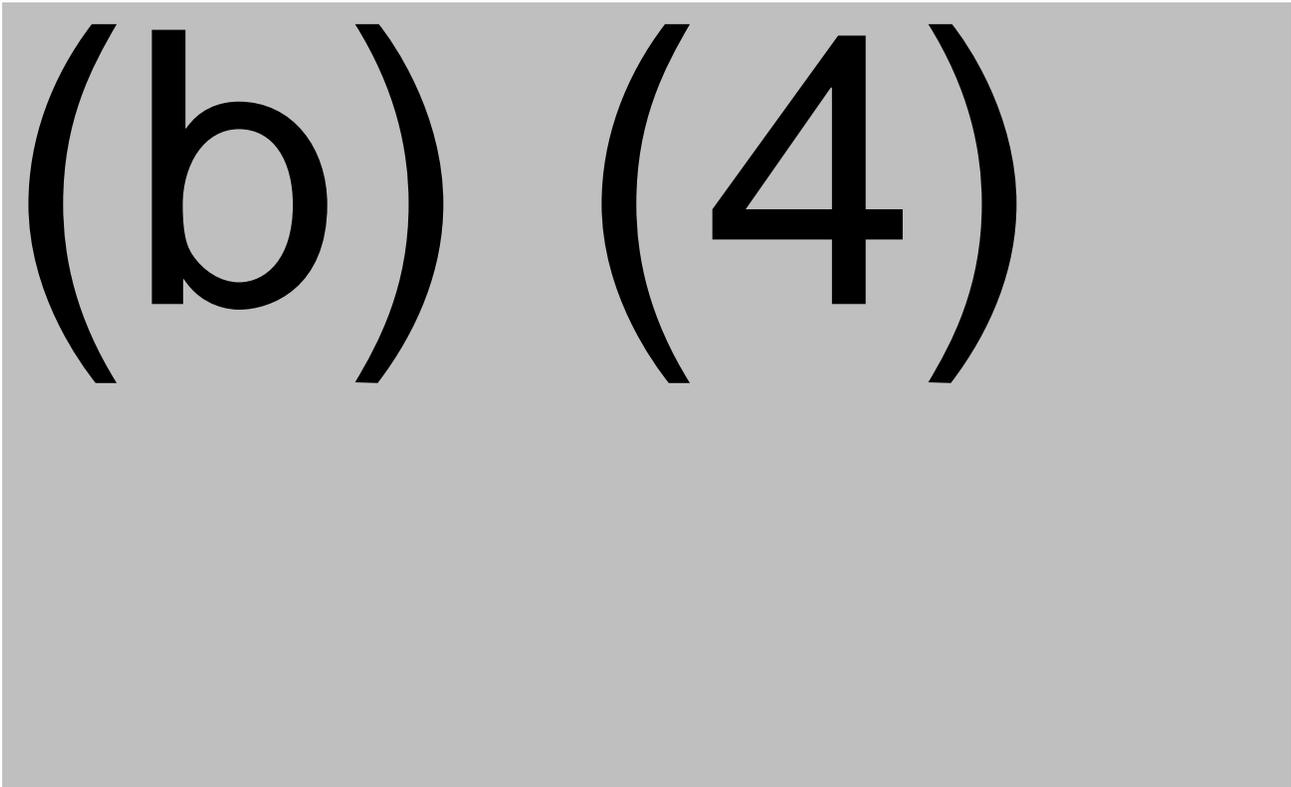
**2. Batch Formula**

The batch formula for IGSC, 20% is as follows and summarizes the quantities of different components required for the preparation for a product lot of (b) (4) in batch size.

Component	Reference to Quality Standard	Amount (kg) for a Batch
Protein	(b) (4)	(b) (4)
Glycine (excipient)	(b) (4)	(b) (4)
(b) (4) (for pH adjustment)	(b) (4)	(b) (4)
Water for Injection (to final volume)	(b) (4)	(b) (4)

EP = European Pharmacopoeia  
USP = United States Pharmacopoeia  
NF = National Formulary

A summary of the in-process controls for the drug product manufacturing are as follows:



**III. Equipment Qualification**

The equipment and critical systems used for IGSC, 20% were qualified for the manufacturing of IGI, 10% licensed under STN 125105. The manufacturing process for IGSC, 20% did not involve any changes to the process and the equipment systems except for changes made in the (b) (4) facility as follows:

- (b) (4)

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(b) (4)

**Reviewer Comments:** The cleaning validation of the tank (b) (4) are acceptable. All deviations were sufficiently justified and closed.

**IV Process Simulations (Media Fills)**

Media fills are performed to support the validation of the aseptic manufacturing process. All manufacturing areas are cleaned and sanitized prior to each sterile fill for routine manufacturing of IGSC, 20%. The same manufacturing equipment for the production of IGSC, 20% is used for filling of the nutrient medium (b) (4). The production procedures for the sterile media fill are specified in the media fill master lot record and are comparable to that of the IGSC, 20% manufacturing process. Personnel that are trained and involved in the product filling operation conduct the aseptic fill runs. Routine EM was performed during the media fills.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

**Reviewer Comments:** The media fills were performed and qualified for the (b) (4) vial types using the filling kit modifications. This was acceptable.

**V. Process Validation**

IGSC, 20% conformance lots were manufactured to validate the process at the (b) (4) facility. The currently licensed upstream process to obtain the intermediate (b) (4) at the (b) (4)

for the IGSC, 20% process. The overall process validation goal was to demonstrate the following:

- A controlled and robust manufacturing process
- Capability of the process to produce IGSC, 20% that consistently met pre-determined specifications
- Capability of the process to manufacture IGSC, 20% that consistently met additional product characterization limits
- Capability to remove process-related impurities through the manufacturing process
- Comparable final product manufactured from (b) (4) originating from (b) (4) for the drug substance

(b) (4)

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(b) (4)

The final product release specifications for IGSC, 20% are as follows:

Test Parameter	Test Method (Reference)	Specification
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Appearance	Visual Inspection	The liquid preparation is clear and colorless or pale yellow or light-brown
Bacterial Endotoxins	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Glycine	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
IgA	(b) (4)	(b) (4)

Test Parameter	Test Method (Reference)	Specification
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Octoxynol 9 (or Triton X-100)	(b) (4)	(b) (4)
pH value	(b) (4)	4.6 to 5.1 : (b) (4)
(b) (4)	(b) (4)	(b) (4)
Polysorbate 80 (or Tween 80)	(b) (4)	(b) (4)
Protein Identity	(b) (4)	(b) (4)
Purity	(b) (4)	(b) (4)
Sterility	(b) (4)	(b) (4)
Total Protein	(b) (4)	(b) (4)
Tri-(N-butyl) Phosphate (TNBP)	(b) (4)	(b) (4)

(b) (4)  
 NLT = not less than, NMT = not more than, (b) (4)

**Deviations**

During the manufacture of the conformance lots, Baxalta experienced deviations which were previously discussed with FDA in the November 12, 2014 Type C meeting. The deviations and proposed corrective actions are described below.

**Deviation #1:** Lower protein content was observed in the last filled vials of all three conformance lots. However all protein results were within the specification. The minimum and maximum protein contents for the three conformance lots are as follows:



Baxter conducted an investigation into the lower protein content deviation. The details and the corrective actions employed are provided in the report ER-TS-14-014.FR.

(b) (4)

(b) (4)

(b) (4)

**Deviation #2:** During the manufacture of batch (b) (4), a reduced flow rate during sterile filtration (b) (4) was observed. Baxter conducted an investigation into the reduced flow rate. The deviation and the corrective actions are detailed in the report ER-TS-14-028.

The root cause was identified to be (b) (4)

Baxter proposes to validate the equipment modifications, and to demonstrate the effectiveness of the two corrective actions (b) (4). Baxter will process three validation lots using IgG solutions (b) (4)

Additionally, Baxter upon implementation of routine manufacturing will monitor the first (b) (4) IGSC, 20% lots manufactured for the purposes of monitoring the effectiveness of the corrective actions as well as the continued process robustness. Specifically, Baxter will monitor the (b) (4)

[REDACTED]  
[REDACTED] of the IGSC, 20% manufacturing process.

**Reviewer Comment:** The corrective actions appear appropriate for the prevention of the (b) (4) which could cause a (b) (4)