



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

Date: June 29, 2016

To: To file for STN BLA 125596/0

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Applicant: Baxalta U.S. Incorporated

Product: Immune Globulin Subcutaneous (Human), 20% solution (IGSC, 20%)

Date: September 14, 2015

Subject: Final CMC review of Baxalta U.S. Incorporated's IGSC, 20% - focused on manufacturing process and analytical methods

Recommendation

The manufacturing process and analytical methods are acceptable with the following recommended Postmarketing Commitments (PMCs):

1. Based on one year of manufacturing experience, please establish specifications for (b) (4), osmolality, (b) (4), (b) (4), and (b) (4) for IGSC, 20% final product. Validation of tests, proposed specifications, and testing data will be submitted as a PAS by July 13, 2017. In the meantime, you may modify your Lot Release Protocol by adding these tests "For Information".
2. Please submit as a PAS the recalibrated (b) (4) assay reported as mIU (b) (4) using the (b) (4) international standard, and a proposed lot release specification based on manufacturing experience, within 12 months of BLA approval (September 13, 2017). In the meantime, please modify your Lot Release Protocol by adding the (b) (4) "For Information."

Executive Summary

The manufacturing process for Baxalta's Immune Globulin Subcutaneous (Human), 20% solution (IGSC, 20%) utilizes very similar manufacturing process as the Immune Globulin Infusion, (Human), 10% (IGI, 10%; STN 125105) licensed under the trade names GAMMAGARD LIQUID (US). IgG preparations are purified from large human plasma pools using a modified Cohn-Oncley cold ethanol fractionation process, as well as cation exchange chromatography. Three dedicated virus reduction steps are solvent/detergent (S/D) treatment, nanofiltration, and incubation at low pH and elevated temperature in the final formulation. The manufacturing process for IGSC, 20% product varies from the licensed IGI, 10% product in the (b) (4), formulation and additional minor differences. The final formulation step is achieved at the (b) (4) against 0.25 M glycine buffer at pH (b) (4) (the solution is concentrated to a protein concentration of minimum (b) (4)) and the further (b) (4) to meet the final release criteria of a pH of 4.6 to 5.1 and a protein concentration of human IgG of (b) (4).

The analytical methods used for IGSC, 20% are mostly the same as for the 10% product. Limits for some antibody tests and contaminants are (b) (4) 10% product's specification and some limits were slightly changed (bacterial endotoxins, (b) (4)). (b) (4), (b) (4), Osmolality and (b) (4) specifications are not included among specifications for IGSC, 20% product. Review of release data for the Sponsor's IGI, 10% has revealed the presence of occasional lots with (b) (4). Some modifications of the IGI, 10% manufacturing process, (b) (4). Since IGSC, 20% and IGI, 10% share nearly identical manufacturing processes, the review team is in agreement that additional measures of (b) (4), osmolality, (b) (4), (b) (4), and (b) (4), and additional clarity in (b) (4) reporting, provide important safeguards for keeping patient risk acceptably low. The following Postmarketing Commitments (PMCs) are recommended (this final version of PMCs was communicated to the Sponsor on May 17, 2016):

1. Based on one year of manufacturing experience, please establish specifications for (b) (4), osmolality, (b) (4), (b) (4), and (b) (4) for IGSC, 20% final product. Validation of tests, proposed specifications, and testing data will be submitted as a PAS by July 13, 2017. In the meantime, you may modify your Lot Release Protocol by adding these tests "For Information".
2. Please submit as a PAS the recalibrated (b) (4) assay reported as mIU (b) (4) using the (b) (4) international standard, and a proposed lot release specification based on manufacturing experience, within 12 months of BLA approval (September 13, 2017). In the meantime, please modify your Lot Release Protocol by adding the (b) (4) "For Information."

Background

On September 14, 2015, Baxalta U.S. Incorporated submitted an original BLA for Immune Globulin Subcutaneous (Human) 20% solution (IGSC, 20%) to treat primary immune deficiency disorders associated with defects in humoral immunity.

This memorandum comprises my review of specific CMC aspects of the original BLA 125596 and focuses on manufacturing process and analytical methods.

It should be noted that while the submission is in the form of a new BLA, the manufacturing process for IGSC, 20% utilizes very similar manufacturing process steps as the Immune Globulin Infusion, (Human), 10% (IGI, 10%, STN 125105) licensed under the trade names GAMMAGARD LIQUID (US) and KIOVIG (EU) with the exception of the (b) (4), formulation step and additional minor differences. The concentration of this product is 20% rather than 10% and the route of administration is subcutaneous. IGI, 10% was approved April 27, 2005.

Specifications for IGSC, 20% have been set in accordance with existing manufacturing data and historical experience gained with GAMMAGARD LIQUID/ Immune Globulin Infusion (Human) and Baxalta, EU Licensed SUBCUVIA (IGSC, 16%).

As a result of the same DP and the limited changes to the manufacturing process as compared to IGI 10%, many of the general BLA review requirements are not applicable to this submission. This memorandum lists manufacturing and analytical methods changes as compared to the IGI, 10% product.

The 20% formulation has been developed to eliminate the need for product reconstitution, infuse a smaller volume for shorter infusion time, provide isotonicity, and buffering capacity while (b) (4) against 0.25 M glycine buffer.

BLA 125105 and IND 14505 are cross-referenced.
The action due date is September 13, 2016.

Review Summary

1. Product Description

Immune Globulin Subcutaneous (Human) 20% solution (IGSC, 20%) is a purified IgG liquid preparation manufactured via a modification of the Cohn-Oncley cold ethanol fractionation process and further purified via weak anion and cation exchange chromatography at 20% w/v protein concentration. The formulation includes 200 mg of protein per mL (20% strength), of which at least 98% is gamma globulin, glycine presented in the range of (b) (4), and water for injection, at pH of 4.6 to 5.11, with no preservatives. IGSC, 20% is supplied in single-dose glass vials that nominally contain 1 g, 2 g, 4 g and 8 g protein per vial. The active biological component is human IgG antibodies derived from pools of human blood plasma, composed of all four IgG subclasses at levels equivalent to those in human plasma. The Fc and Fab functions are maintained in IGSC, 20%, while (b) (4).

2. Manufacture

(a) Manufacturing Process Overview

(b) (4)

(b) (4)

(b) (4)

(b) Manufacturing – comparison to the licensed IGI, 10%

Flow Charts including production steps, equipment, material and in-process tests are included in the original submission. IGSC, 20% is manufactured by a (b) (4). The steps (b) (4) are described in DS section of the submission. Formulation and low pH incubation steps (Step (b) (4)) are described in DP section of the submission. A flow diagram of the IGSC, 20% manufacturing process steps (b) (4) is provided in Figure 1. The downstream steps for DP are described in the continuation of Figure 1 (step numbers in brackets refer to numbering continuing from manufacturing of the DS).

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

(c) Manufactures

Fractionation of plasma and (b) (4) production occurs in the currently licensed facilities in (b) (4). Further processing of (b) (4) batches from these three facilities occurs in (b) (4), where (b) (4) batches are combined and purification of (b) (4) to final product occurs. The manufacturing rooms in (b) (4) are shared with other products.

(d) Analytical Methods

The test parameters, test methods and release specifications for IGSC, 20% are provided in Table 3. The specifications for the 20% product have been set based on a combination of compendial limits, existing manufacturing data, historical experience with GAMMAGARD/ KIOVIG LIQUID (IGI, 10%) and Baxalta, EU Licensed SUBCUVIA (IGSC, 16%).

Table 3. Test Parameters, Test Method and Final Product Release Specifications for IGSC, 20%

| 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) |
| (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) | Satisfactory |
| 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)

i. Comparison of the specifications of the IGSC, 20% and licensed IGI, 10%

The changes in specifications of the IGSC, 20% as compared to the IGI, 10% (based on the most recent AR for IGI, 10%, STN 125105/1414, received 3/18/2016) product are noted in *italics*.

- Appearance: “*Light brown*” specification is added and “slightly opalescent” specification is removed from the appearance specification for IGSC, 20% product as compared to 10 % product.
- Bacterial Endotoxins: Specification changed from (b) (4) for IGSC, 20% product.
- Glycine: The specification is changed from (b) (4) for the 20% product.
- (b) (4) : (b) (4)
- The limits for following specifications are (b) (4):

(b) (4)
 (b) (4)
 IgA – (b) (4)
 Octoxynol 9 (or Triton X-100) – (b) (4)
 (b) (4) *times the antibody level* of CBER Reference
 (b) (4)
 (b) (4)
 (b) (4)
 Polysorbate 80 (or Tween 80) – (b) (4)

- The following specifications are not changed:

(b) (4) ; pH; Protein Identity; Purity;
 Sterility

- The following specifications are not listed for Drug Product Specifications for the 20% product but are used for the 10% product:

(b) (4)
 (b) (4)
 Osmolality by osmometry: (b) (4)
 (b) (4)

The sponsor notes that *the IGSC, 20% process has been demonstrated to be capable of removing/reducing these impurities to acceptable levels:* (b) (4)

The Sponsor is relying on preclinical and clinical safety data generated with IGI, 10% to support the IGSC, 20% product. On that basis, the specifications for the IGSC, 20% product should be entirely based on those for the IGI, 10% product, unless the Sponsor has data set to show that the changed specifications for IGSC, 20% assure safety, purity, potency, and effectiveness of the product in a manner equal to or greater than the standards already in place for the product (21 CFR 610.9).

In the 2005 justification of IGI, 10% specifications, the Sponsor noted that (b) (4). On that basis an upper limit on (b) (4) was proposed and accepted. (b) (4) also has

(b) (4). An upper limit on (b) (4) was proposed and accepted. For some patients, high or low osmolality may trigger undesirable infusion reactions. A range for osmolality of IGI, 10% was proposed and accepted. (b) (4) is associated with adverse reactions in some patients. An upper level of (b) (4) was proposed and accepted. The omissions proposed by the Sponsor do not seem to be sufficiently supported by the data submitted in the original BLA125596.

ii. Review of release data for the Sponsor's IGI, 10% has revealed the presence of occasional lots with (b) (4). Since IGSC, 20% and IGI, 10% share nearly identical manufacturing processes, the review team is in agreement that additional measures of manufacturing consistency, and additional clarity in (b) (4) reporting, provide important safeguards for keeping patient risk acceptably low.

Returning (b) (4), osmolality, (b) (4), and (b) (4) specifications to the release testing for IGSC, 20%, as additional measures of manufacturing consistency within 6 months after BLA approval and the calibrated (b) (4) assay using a (b) (4) international standard were discussed with the Sponsor during a teleconference on April 21, 2016. In response, the sponsor provided justification (Amendment 125596/0.20) for not including (b) (4), Osmolality and (b) (4) as release specification for IGSC, 20%.

The review team reviewed the provided justifications for excluding measurements of (b) (4) and osmolality as release specifications and conveyed to the sponsor that IG delivered by subcutaneous route still has the potential for adverse events related to thrombogenicity. The team agreed that measurements of (b) (4) and osmolality are useful measures of the product's quality and consistency. Information from these tests may aid in rapid identification of outlier lots, which could further limit patient risk. These considerations outweigh a desire to streamline specifications based on the Ph. Eur. monograph, or desire for a harmonized global specification. With these considerations in mind, the following commitments post-marketing are requested:

- 1) Based on one year of manufacturing experience, please establish specifications for (b) (4), osmolality, (b) (4) for IGSC, 20% final product. Validation of tests, proposed specifications, and testing data should be submitted as a PAS within 10 months of BLA approval. In the meantime, you may modify your Lot Release Protocol by adding these tests "For Information."
- 2) Please calibrate the (b) (4) assay using the (b) (4) international standard, with results reported as mIU (b) (4). In the meantime, you may modify your Lot Release Protocol by adding the (b) (4) "For Information." The recalibrated assay, and a proposed lot release specification based on manufacturing experience, will be submitted within 12 months of BLA approval.

Conclusion

The manufacturing process is very similar to the licensed IGI, 10% product and seems to be acceptable. Most of the noted differences between the new 20% product and the licensed 10% product are based on the specifics related to the 20% preparation and the higher concentration product. Regarding (b) (4) maintain these assays given that the Sponsor relies on data generated with the (b) (4) product to support the IGSC, 20% product. The omitted specifications and the calibrated (b) (4) assay using a (b) (4) international standard will need to be included in the release testing for IGSC, 20% as requested in PMCs:

- 1) Based on one year of manufacturing experience, please establish specifications for (b) (4), osmolality, (b) (4) for IGSC, 20% final product. Validation of tests, proposed specifications, and testing data should be submitted as a PAS within 10 months of BLA approval. In the meantime, you may modify your Lot Release Protocol by adding these tests “For Information.”
- 2) Please calibrate the (b) (4) assay using the (b) (4) international standard, with results reported as mIU (b) (4). In the meantime, you may modify your Lot Release Protocol by adding the (b) (4) “For Information.” The recalibrated assay, and a proposed lot release specification based on manufacturing experience, will be submitted within 12 months of BLA approval.