



CBER REGULATORY REVIEW MEMORANDUM

Date 7 July, 2016

From Claire H. Wernly, Ph.D.
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biologics License Application: Submission Tracking Number # 125596/0

Subject BLA: Review of Sterility and Bacterial Endotoxins Test Qualifications for Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%). Review of the appropriate use of the CBER Standard (b) (4) (for use in *in-vivo* (b) (4) assays) in the (b) (4) Content, (b) (4) (*in-vitro*) Assay.

Through James L. Kenney, D.Sc., Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA
William M. McCormick, Ph.D., Director, DBSQC/OCBQ/CBER/FDA

Applicant Baxalta USA Inc.

Product Immune Globulin Subcutaneous (Human), 20% (IGSC, 20%).

Biologics License Application (BLA) Submission Tracking Number (STN) 125596/0

Submission Received by CBER 14 September, 2015

Review Completed 7 July, 2016

Material Reviewed

Method qualifications for: 1) sterility, (2) endotoxin and 3) (b) (4) content, (b) (4) (*in-vitro*) (b) (4) tests performed on the drug product for Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%).

Executive Summary

After a thorough review of this BLA, and the response to CBER's Information Request (IR) (Amendment 125596/0.1 - received on 14 October of 2015), this reviewer finds Baxalta's sterility and endotoxin test methods were qualified in accordance with (b) (4) respectively, by

demonstrating the IGSC, 20% matrix is suitable for these intended test methods. This reviewer finds the use of the CBER's U.S Standard (b) (4) for (b) (4) (for *in-vivo* use only) for use in the (b) (4) content, (b) (4) (*in-vitro*) assay acceptable, as currently there is no official international standard calibrated for use in this alternate potency method.

Background

On 14 September, 2015, Baxalta submitted a BLA for IGSC, 20%, a sterile, highly purified, human, polyvalent immunoglobulin G (IgG) solution containing concentrated (approximately 200mg of protein [at least 98% of which is gamma globulin] per mL) human IgG collected from human plasma present in the donor population. As a result, IGSC 20% contains a broad spectrum of antibody specificities against various bacterial, viral, parasitic and mycoplasma antigens, that are capable of opsonization and neutralization of various microbes and toxins.

IGSC, 20% is indicated as replacement therapy for the treatment of primary immunodeficiency disorders (e.g., common variable immunodeficiency, X-linked agammaglobulinemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome) associated with defects in humoral immunity in adult and pediatric patients two years of age and older. The recommended dose (administered via subcutaneous infusion at regular intervals from daily up to biweekly) is individualized based on the patient's pharmacokinetic and clinical response as monitored through serum IgG through levels.

IGSC, 20% uses a similar manufacturing process to the currently licensed GAMMAGARD LIQUID IGI, 10% (Immune Globulin Infusion, [Human]) product (STN: 125105) with the exception of the (b) (4) and formulation steps, route of administration (subcutaneous [SC] vs. intravenous [IV]) and final concentration (20% vs 10%). IGSC, 20% is manufactured in a (b) (4); therefore a (b) (4). (b) (4) undergo a low pH incubation step (30° C to 32° C for (b) (4)) as a (b) (4) viral inactivation step.

The final product is supplied as a single dose (200 mg/mL [i.e., 20%]) presented in single-dose vials containing one of the following grams of protein/vial fill sizes of: 1g/5 mL, 2g/10 mL, 4g/20 mL and 8g/40mL. Additional components include glycine as a stabilizing agent (b) (4) and water for injection. There are no preservatives.

The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also produces and calibrates CBER's U.S. Standard (b) (4) for (b) (4) and (b) (4) test methods; therefore DBSQC has expertise in these *in-vivo* and *in-vitro* test methods, reviews them to ensure regulatory compliance, and their use of the CBER reference standards are appropriate for the intended test method, which also provides quality control production oversight of CBER standard replacement lots. These review activities also support CBER's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on the: 1) sterility and 2) (b) (4) bacterial endotoxin (b) (4) test methods performed on the DP and 3) the appropriate use of CBER's U.S. Standard (b) (4) for (b) (4) (for *in-vivo* use only) for use in the (b) (4) assay.

Review

Sterility Test Qualification

Baxalta qualified their IGSC, 20% DP matrix using the (b) (4) method by performing (b) (4) qualification studies on one lot (i.e., lot number: (b) (4)) to demonstrate their DP matrix is suitable for the intended test method.

(b) (4)



(b) (4)



Endotoxin Test Qualification

Baxalta qualified their (b) (4) test method on three lots (i.e., lot numbers: (b) (4)) to demonstrate their DP matrix is suitable for the intended test method.

(b) (4)



CBER finds Baxalta's (b) (4) method was qualified in accordance with (b) (4) by demonstrating the DP matrix is suitable for their intended test method and its release specification is acceptable.

(b) (4)

Regardless of the above mentioned concerns, CBER is committed to advancement in scientific alternate methods that reduce, refine or replace the use of animals in assay methods and understands the necessity for an international standard for this (b) (4) assay.

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds Baxalta's sterility and (b) (4) methods were qualified in accordance with (b) (4), respectively, by demonstrating their DP matrix is suitable for these intended test methods. This reviewer finds the use of the CBER's U.S. Standard (b) (4) (for *in-vivo* use only) for use in the (b) (4) Content, (b) (4) (*in-vitro*) assay, acceptable as currently there is no official international standard calibrated for use in a (b) (4) Assay.