



**CBER REGULATORY REVIEW MEMORANDUM**

**Date** 15 May, 2019

**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 # 125683/0

**Subject** BLA: Review of Sterility, Rabbit Pyrogen and Diphtheria Antitoxin Potency Test Method Qualifications for Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%).

**Through** James L. Kenney, D.Sc., Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA  
Maryna Eichelberger, Ph.D., Director, DBSQC/OCBQ/CBER/FDA

**Applicant** Grifols Therapeutics LLC

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

**Biologics License Application (BLA) Submission Tracking Number (STN) 125683/0**

**Submission Received by CBER** 09 July, 2018

**Review Completed** 15 May, 2019

**Material Reviewed**

Method qualifications for: 1) sterility, 2) rabbit pyrogen and 3) diphtheria antitoxin potency tests performed on the drug product for Immune Globulin Subcutaneous (Human), 20% (IGSC, 20%); and the response to CBER's Information Requests (IRs), received on 22 February, 25 March and 10 May of 2019 were also reviewed.

**Executive Summary**

After a thorough review of this BLA, and the response to CBER's IRs (amendments 125683/0.23, 125683/0.26 and 125683/0.34 - received on 22 February, 25 March and 10 May of 2019 respectively), this reviewer finds Grifols' sterility test method was qualified in accordance with (b) (4) and the

rabbit pyrogen test method was performed appropriately in accordance with USP (b) (4), by demonstrating the IGSC 20% matrix is suitable for these intended test methods. In addition, their diphtheria antitoxin potency test is compliant with (b) (4). This reviewer finds the use of the CBER's U.S Standard Diphtheria Antitoxin for (b) (4) in the Diphtheria Antitoxin content, (b) (4) assay acceptable. However, CBER recommended that Grifols requalifies their (b) (4) assay using the official (b) (4) for use in a Diphtheria (b) (4) Potency Assay available from (b) (4) (i.e., Diphtheria Antitoxin Human IgG (b) (4)).

## Background

On 09 July, 2018, Grifols' submitted a BLA for IGSC 20%, a clear to slightly opalescent and colorless to pale yellow (b) (4) solution, sterile, highly purified, human (b) (4) immunoglobulin G (IgG) solution containing concentrated human IgG purified from human plasma collected from a large number of donors. 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 treatment of primary humoral 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 using an infusion pump at regular intervals from daily up to biweekly) is individualized based on the patient's pharmacokinetic and clinical response as monitored through serum IgG levels.

IGSC 20% is supplied as a single dose (0.2 g/mL [i.e., 200 mg/mL; 20%]) presented in single-dose vials containing one of the following grams of protein/vial fill sizes: 1 g/5 mL, 2 g/10 mL, 4 g/20 mL and 10 g/50 mL.

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 Diphtheria Antitoxin for Neutralization and flocculation test methods; therefore, DBSQC has expertise in these *in-vivo* and *in-vitro* test methods, reviews them to ensure regulatory compliance and that their use of the CBER reference standards is appropriate for the intended test method. 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 sterility, rabbit pyrogen and diphtheria antitoxin potency test methods performed on the IGSC 20% drug product (DP).

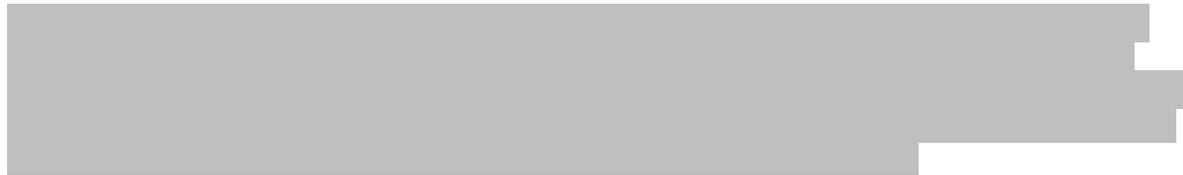
## Review

### Sterility Test Qualification

(b) (4)



(b) (4)



Rabbit Pyrogen Test

The rabbit pyrogen test is a compendial test that does not require suitability qualification testing; however, the method (standard operating procedure [i.e., CS-000BB-125]) was reviewed to ensure it performed in accordance with USP (b) (4). In addition, Grifols submitted the rabbit pyrogen test results for (b) (4) batch conformance lots (lots: (b) (4) of their IGSC, 20% DP and the results were found to be accordance with the USP (b) (4) specifications, indicating an absence of pyrogens in the final container product.

Diphtheria Antitoxin Potency Test

(b) (4)



(b) (4)



### Conclusions

After a thorough review of this BLA, this reviewer finds Grifols' sterility test method was qualified in accordance with (b) (4) and the rabbit pyrogen test method was performed appropriately in accordance with USP (b) (4), by demonstrating the IGSC 20% matrix is suitable for these intended test methods. In addition, their diphtheria antitoxin potency test is compliant with (b) (4). This reviewer finds the use of the CBER's U.S Standard Diphtheria Antitoxin for (b) (4) in the Diphtheria Antitoxin content, (b) (4) assay acceptable. Upon CBER's recommendation, Grifols' has committed to requalify their (b) (4) assay using the (b) (4) calibrated for use in a Diphtheria (b) (4) Potency Assay available from (b) (4) (i.e., Diphtheria Antitoxin Human IgG (b) (4) and submit new qualification report as part of a PAS.