



## CBER REGULATORY REVIEW MEMORANDUM

**Date** 15 April, 2016

**From** Simleen Kaur  
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 # 125590/0

**Subject** BLA: Review of Bioburden, Sterility, Endotoxin, Pyrogen and Diphtheria Tests for Immune Globulin Intravenous (Human), 10% Liquid (RI-002)

**Through** Dr. James L. Kenney, Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA  
Dr. William M. McCormick, Director, DBSQC/OCBQ/CBER/FDA

**Applicant** ADMA Biologics, Inc. (ADMA)

**Product** Immune Globulin Intravenous (Human), 10% Liquid (RI-002)

**Biologics License Application (BLA) Submission Tracking Number (STN)** 125590/0

**Submission Received by CBER** 31 July, 2015

**Review Completed** 15 April, 2016

### Material Reviewed

Method qualifications for: 1) bioburden; 2) sterility; and 3) endotoxin tests performed on RI-002. In addition, procedures for pyrogen and diphtheria tests and information request response received 28 October and 13 November of 2015 and 08 January, 05 February and 22 March of 2016 were also reviewed.

### Executive Summary

After a thorough review of this BLA, this reviewer finds the bioburden, sterility, and endotoxin test methods were qualified in accordance with (b) (4) respectively. In addition, diphtheria and pyrogen tests are being performed in accordance with (b) (4) and 21 CFR 610.13(b), respectively for RI-002.

## Background

On 31 July, 2015, ADMA submitted this BLA for RI-002 for treatment of primary immunodeficiency diseases. RI-002 is a human immunoglobulin product supplied as a solution for intravenous infusion. It contains 10% Immunoglobulin G  $\geq 96\%$  purity formulated with sodium chloride, glycine, and polysorbate 80 at a pH of  $4.3 \pm 0.3$ . The manufacturing of RI-002 is divided into two contract manufacturers: Biotest Pharmaceuticals, Inc. (Biotest) for Drug Substance (DS) and (b) (4) for Drug Product (DP).

The manufacturing of DS at Biotest starts with (b) (4)

(b) (4)


The 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 reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. In addition, since DBSQC produces and calibrates CBER toxin and antitoxin reference standards used in *in-vivo* and *in-vitro* test methods; DBSQC has expertise in these methods and reviews them to ensure regulatory compliance. Therefore, DBSQC's review of toxin/antitoxin methods ensures reference standard use is appropriate for the intended test method and provides quality control production oversight of CBER potency standard replacement lots, if applicable. These review activities support DBSQC's lot-release mission: the confirmatory testing of submitted product samples; review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications; and the production, maintenance and distribution of CBER Standards and Reagents. Therefore, this review will focus on the method qualification for ADMI's bioburden, sterility and endotoxin methods to ensure the product matrix is suitable for these intended test methods and the review of their diphtheria and pyrogen test procedures to ensure they are compliant with the (b) (4) and 21 CFR 610.13(b).

## Review

(b) (4)

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(b) (4)



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#### Sterility Test Qualification for DP

ADMA qualified their RI-002 DP matrix using the (b) (4) method by performing bacteriostatic and fungistatic qualification studies on (b) (4) lot (i.e., lot number: (b) (4)) to demonstrate the DP matrix is suitable for the intended test method. The test was performed according to (b) (4) using the (b) (4) sterility method and (b) (4) indicator microorganisms (b) (4),

(b) (4)

The test for each microorganism was performed using (b) (4)

(b) (4)

ADMA submitted sterility test on (b) (4) clinical and stability DP lots (b) (4) and results were found to be in compliance with (b) (4)

#### Pyrogen test for DP

CBER reviewed the Standard Operating Procedure (SOP), 16E-02: “Pyrogen Test (Rabbit)”, provided in the original submission. The SOP was found to be in accordance with (b) (4) and 21 CFR 610.13.

ADMA performed the rabbit pyrogen test on (b) (4) clinical and stability DP lots (i.e., (b) (4)) and results were found to be in compliance with 21 CFR 610.13(b).

#### Diphtheria (b) (4) test for DP

Diphtheria (b) (4) test is performed by (b) (4) CBER reviewed the Standard Operating Procedure (SOP) from (b) (4), QM/1143/03: “Diphtheria Antitoxin Assay”, provided in the original submission. The SOP was found to be in accordance with (b) (4).

ADMA submitted diphtheria results on (b) (4) clinical and stability DP lots (i.e., (b) (4)) ranging from (b) (4), which met their diphtheria test specification of (b) (4)

#### **Conclusion**

After a thorough review of the information submitted in this BLA, this reviewer finds ADMA RI-002 DP matrix is suitable for testing using their sterility, as the test was qualified and performed in accordance with (b) (4). Diphtheria and pyrogen tests on DP matrix are being performed in accordance with (b) (4) and 21 CFR 610.13(b), respectively. In addition, the RI-002 (b) (4) matrix is suitable for testing using their bioburden and endotoxin test methods and the qualification was performed in accordance with (b) (4) respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.