MEMORANDUM

To: Review Committee Chair, STN 125590/0

From: Leslyn Aaron, Biologist, LACBRP, DBSQC, OCBQ

Through: Lokesh Bhattacharyya, PhD, Chief, LACBRP, DBSQC, OCBQ

               Maryna Eichelberger, PhD, Division Director, DBSQC/OCBQ

Sponsor: ADMA Biologics, Inc.

Product: Immune Globulin Intravenous (Human) 10% Liquid, Asceniv™

Subject: BLA Review Memo for Lot-Release Test Method for the (b) (4)
               assay in the Immune Globulin Intravenous (Human) 10% Liquid,
               RI-002 Drug Product (Asceniv™ proposed trade name)

Recommendation: Approval

Summary of Review

This document constitutes the review memo for the Biological License Application
(BLA), for STN 125590/0, submitted by ADMA, for the Determination of (b) (4)
due to (b) (4) -like impurities present in RI-002 drug product. Based on the
information submitted, the method has been described and validated adequately and
can be approved for its intended use.

Background

RI-002 drug product is indicated for use in patients with primary immunodeficiency
disease (PID). It is a clear to slightly opalescent and colorless, sterile, nonpyrogenic
injectable solution of normal human immunoglobulin G (IgG) and comprises at least
96% normal human IgG formulated in glycine, sodium chloride, polysorbate 80, and
Water for Injection (WFI) and is presented as 100 mg IgG/mL.

The initial submission of STN 125590/0 received Complete Response (CR) letter, which
was issued to the sponsor on July 29, 2016. In this submission, the results showed that
many of the validation characteristics did not meet their respective acceptance criteria.
In the response to the CR letter (125590/0.42), the sponsor informed that they would
submit an (b) (4) assay that would demonstrate higher sensitivity as
compared to the (b) (4) assay and allows for sample dilutions to address matrix effects.

In STN 125590/0.51, ADMA submitted (b) (4) ▊▊▊▊▊▊▊▊▊▊▊
▊▊▊▊▊▊▊▊▊▊▊ Test Method and its validation.

Submitted Information and Documents

Information reviewed includes:

- 125590\0.51 – Response to FDA Request for Information dated February 12, 2019
  - ✓ 3.2.P.5.1 Analytic Procedures
    - ▪ (b) (4) ▊▊▊▊▊▊▊▊▊▊▊
      - • TM-10058-2 – (b) (4) ▊▊▊▊▊▊▊▊▊▊▊▊▊
        ▊▊▊ Test Method for 101801 IVIG DP (b) (4)
  - ✓ 125590\0.51 – 3.2.P.5.3 Validation of Analytic Procedures
    - ▪ Validation of Analytical Procedures - (b) (4) ▊▊▊▊▊▊▊
      - • AMVR-20181204-01 – (b) (4) ▊▊▊▊ Test Method for 101801 IGIV
        DP (b) (4)
  - ✓ 125590\0.57 – 3.2.P.5.3 Validation of Analytic Procedures
    - ▪ Validation of Analytical Procedures - (b) (4) ▊▊▊▊▊▊▊▊▊
      - • Validation of Analytical Procedures [RI-002, ADMA Biologics]
        (b) (4) ▊▊▊▊▊▊▊

Review Narrative

Method

(b) (4) ▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊▊
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(b) (4)

Information Requests and Review of Responses

The information requests referenced below were submitted to the sponsor on March 4, 2019. The sponsor's responses were received on March 14, 2019 as Amendment 125590/0.57. The IRs and review of the responses are detailed below:

1. Please provide a summary of the differences between the (b) (4) Assay Test Method for Biotest Pharmaceuticals Immune Globulin Drug Product (TM-10011) and the (b) (4) Test Method 101801 IVIG DP (b) (4) (TM-10058).

   Review of the Response: The sponsor provided a summary of the differences between the (b) (4) test method (TM-10011) and the (b) (4) test method (TM-10058).

2. In 125590/0.51, Response to FDA Request for Information, dated February 22, 2019 you reported linearity by plotting geometric mean of measured (b) (4) vs (b) (4) Linearity should be determined by (b) (4) Please submit your linearity results from plots of response vs activity for both standard and sample, and evaluation of parallelism between the standard and sample dilution curves for the (b) (4) Test Method 101801 IVIG DP (b) (4) (TM-10058).

<u>Review of the Response</u>: The sponsor provided a comparison of the results of (b)(4) lot of DP spiked to (b)(4) levels of (b) (4) and the (b) (4) Standard Curve.   The submitted figure shows that the plots are overlapping.

3. The LOQ is the lowest point where an analyte in a sample can be quantitatively determined with adequate precision and accuracy. In your assessment of LOQ you reported the activity of the lowest level (b) (4) of the reference standard curve which met the criteria for accuracy and precision as your LOQ. However, LOQ determination should include analysis of the drug product, as you are measuring the activity in the drug product. Please provide accuracy and precision results from the evaluations of the drug product (DP) to demonstrate that the (b) (4) method can adequately measure DP at (b) (4)

    <u>Review of the Response</u>: The (b) (4) for unspiked DP cannot be determined using the (b) (4) as the (b) (4) values were below the lowest concentration of the standard (b) (4) in the standard curve. As such, the lowest spiked drug product sample level that passes the acceptance criteria for Precision and Accuracy is (b) (4) . The sponsor agrees to revise the test procedure (TM 10058) and the validation report to include LOQ as (b) (4)

4. In the assessment of the range of the method, you presented your reported LOQ as the lowest point of your assay range. While your approach is acceptable, please re-evaluate the range of your method if the assessment of LOQ of your (b) (4) method for the drug product as requested above results in a different LOQ.

    <u>Review of the Response</u>: The sponsor agrees to revise TM-10058 and the validation report to include the assay range as (b) (4)