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**To:** STN: #125590/0

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**Subject:** Review Memo for Biological License Application Amendment, STN125590/0.47, for Human Immunoglobulin, RI-002, from ADMA Biologics, Inc.

**Recommendation:** Approval

### Summary of Review

This memo constitutes the review of ADMA's response to Question#1 of the Information Request submitted on December 11, 2018, related to the (b) (4) method for the determination of total protein, and its validations, as used for the lot release testing of (b) (4) RI-002 (b) (4) drug product.

Based on the information from the previous submissions, and Amendment 0.47, the (b) (4) method is validated adequately for its intended purpose, and approvable for the lot release test of RI-002 (b) (4) drug product.

### Background

RI-002 drug product is a 10% human immunoglobulin G solution for intravenous infusion and intended for the treatment of primary immunodeficiency diseases. Based on the information provided in the original BLA submission, the following analytical methods were recommended for approval for the lot release testing of IR-002 drug product: i) Purity by (b) (4), ii) Protein by (b) (4) Method, iii) Polysorbate 80 Assay, and iv) Particulate Matter. However, a CR letter was issued on July 29, 2016; and on September 28, 2018, ADMA Biologics submitted response to the CR letter.

### Submitted Information reviewed:

125590/0.47 (Amendment) – Recd 12/26/2018 – DATS# 781920

-1.11.1 Quality Information Amendment

- Response to FDA Request for Information – Testing and Analytical Assays-  
11 Dec 2018

- 3.2.P.5. Control of Drug Product

-3.2.P.5.2. Analytical Procedures

- Analytical Procedures - Particulate Matter
- Analytical Procedures – Polysorbate 80
- Analytical Procedures – Protein by (b) (4) Assay
- 3.2.P.5.3. Validation of Analytical Procedures
  - Validation of Analytical Procedures – Protein by (b) (4) Assay

### **Review Narrative:**

The following IR question was submitted on December 11, 2018 to seek additional information regarding the resubmission:

Please provide a complete list of changes you made in all the analytical assays used for RI-002 (b) (4) drug product final container since the issuance of the CR letter dated July 29, 2016.

#### Review of the Response:

As response to the IR, ADMA submitted Amendment 47 on December 26, 2018, in which changes made to the analytical methods after the issuance of the CR letters were listed: no changes were made to the following methods: i) Purity by (b) (4) (b) (4) ii) Polysorbate 80 Assay, and iii) Particulate Matter; while the dynamic range of the method standard curve was changed from (b) (4) (b) (4) for Protein by (b) (4) Method.

To implement the change, calibration standards of (b) (4) (b) (4) are used in the (b) (4) method instead of calibration standards of (b) (4) (b) (4). In the original submission, the (b) (4) method has been validated for RI-002 drug product with a working range of (b) (4) (b) (4), and LOQ of (b) (4) (b) (4). In the resubmission, the range of the calibration standards was altered to (b) (4) (b) (4) without any changes in any assay validity criteria or any other assay procedures, therefore, the working range of (b) (4) (b) (4) for RI-002 drug product is still validated. In this Amendment, a working range of (b) (4) (b) (4) was proposed for RI-002 drug product, which is within the (b) (4) (b) (4) range, and also encompasses the (b) (4) (b) (4) of the release specification (b) (4) (b) (4) before (b) (4) (b) (4) dilution); thus, the new proposed assay range is considered validated.

#### Conclusion

Based on the information provided in the Amendment 0.47, it can be concluded that the (b) (4) (b) (4) method is still validated for the lot release testing of RI-002 drug product .