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To STN: #125590/0

Through William M. McCormick, Director, DBSQC/OCBQ

Product Human immunoglobulin (10%), RI-002

Sponsor ADMA Biologics, Inc.

Subject: Addendum Review Memo for Quality Control Lot-release Tests for the Human Immunoglobulin (10%) Drug Product

Summary of Review

This document constitutes the Addendum Review Memo for the new BLA (STN#125590) submitted for by ADMA Biologics, Inc. for Human Immunoglobulin (10%). LACBRP/DBSQC has been assigned to review the following analytical methods used in lot release of the drug product and their validations.

1. (b) (4)
2. Purity by (b) (4)
3. Protein Assay by (b) (4) Method
4. Polysorbate 80 Assay
5. Determination Particulate Matter

We have reported in the Primary Discipline Review memo (dated 24 March 2016) that assay numbers 2-4 listed above are approvable as lot release tests for the drug product. However, there were outstanding Information Requests (IR) at that time for the (b) (4) assay and the method for the Determination Particulate Matter. We received complete response to our IR for the method for the Determination Particulate Matter since then, which is reviewed in this memo, and the method is found to be approvable. However, the sponsor has not provided complete response to our IRs on method validation for the (b) (4) assay. Thus, we cannot conclude that the (b) (4) assay can be approved.

The review committee has decided to issue a Complete Response (CR) Letter because ADMA's contract manufacturer (Biotest) is under a Warning Letter (WL) and their re-inspection failed to demonstrate that the WL can be withdrawn. Therefore, they will remain

under a compliance hold. The unaddressed IR will be added to the Complete Response Letter.

Background

The new BLA (STN#125590) was submitted for human immunoglobulin (10%), RI-002, by ADMA Biologics, Inc. for the treatment of primary immunodeficiency diseases. The final formulated product is a clear to slightly opalescent, colorless, sterile, nonpyrogenic injectable solution of normal human immunoglobulin G (IgG) and is supplied as a solution for intravenous infusion. The drug product contains 10% (100 mg/mL) protein, of which at least 96% is Immunoglobulin G formulated with 120 ± 20 mM sodium chloride, 245 ± 45 mM glycine and $0.2 \pm 0.05\%$ polysorbate 80 at a pH of 4.3 ± 0.3 .

At the time of writing the Primary Discipline Review memo (dated 24 March 2016) there were outstanding Information Requests (IR) for the (b) (4) assay and the method for the Determination Particulate Matter. We concluded that all other quality control lot-release tests, we reviewed, were approvable. We received responses to our IRs for the (b) (4) assay and the method for the Determination Particulate Matter since then, which were reviewed and discussed in this memo (Final Memo).

Submitted Information Reviewed

This is an electronic submission. Information submitted and reviewed includes:

- 125590\0 – 3.2.P.5.1 Specifications (drug product)
- 125590\0 – 3.2.P.5.1 Description and Composition of the Drug Product
- 125590\0.30 – 1.11.1 Quality Information Amendment – Response to FDA Request for Information – 08 Mar 2016; received on
 - Report – 20160129 Summary Report for (b) (4)
 - ALIR-2014-007 (b) (4) stability
 - ALIR-2014-006 Summary of OOS Test Result, (b) (4) month stability
- 125590\0.33 – 1.11.1 Quality Information Amendment – Section 2. Verification of the Suitability of the Test for Particulate Matter; received on 29 April 2016

Review Narrative

1. (b) (4)
- [REDACTED]

1 page determined to be not releasable: (b)(4)

(b) (4)

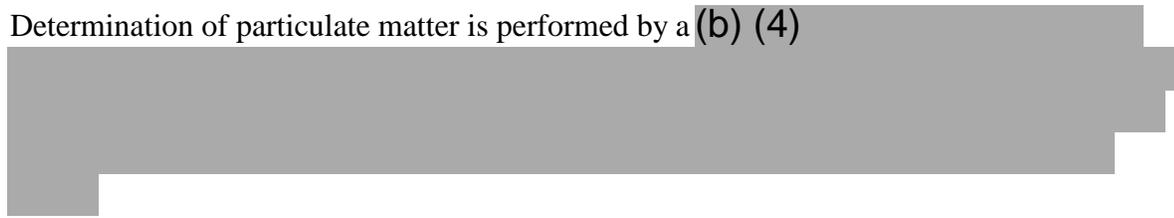
A large rectangular area of the document is completely redacted with a solid grey fill. The text "(b) (4)" is visible in the top-left corner of this redacted area.A rectangular area of the document is completely redacted with a solid grey fill.A rectangular area of the document is completely redacted with a solid grey fill.

Conclusion

The sponsor has not provided complete responses to our IR on method validation. Therefore, this method cannot be considered approvable at this point.

2. Determination Particulate Matter by (b) (4)

Determination of particulate matter is performed by a (b) (4)

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Information Request and Review

The following IR was submitted to the sponsor on 6 March 2016. The sponsor's response was obtained on 29 April 2016 as Amendment 33.

- In response to our previous IR dated 9 November 2015, you provided summary of your instrument qualification. Your response has not addressed our request for verification of suitability of the Test for Particulate Matter to include repeatability and intermediate precision for the RI-002 Injection. Please submit the requested information.

Review of Response: (b) (4) verified method repeatability and intermediate precision using vials of RI-002 drug product. This is appropriate because this test is to be performed by (b) (4).

ADMA's procedure requires testing (b) (4)

[Redacted]

[Redacted]

[Redacted]

Conclusion

While pre-acceptance criteria for Repeatability and Intermediate Precision were not stated by ADMA for this evaluation, the results submitted by ADMA are reasonable and serve to establish the performance of the method under conditions of use as requested. It should be noted that the average values obtained for intermediate precision or (b) (4) are significantly below the product specification of (b) (4)

(b) (4) . The procedure is adequately described, consistent with (b) (4) and includes appropriate calibration and system suitability requirements.

CR Letter

We recommend that the Following outstanding issue on the (b) (4) Assay be included in the CR Letter.

- You have presented the results of the intermediate precision study as evidence of robustness of the (b) (4) Assay Test Method for IVIG Drug Product. This data is insufficient to demonstrate method robustness. Please provide data to evaluate effect of small deliberate changes of critical method parameters, such as reagent concentration, incubation time, etc. in order to demonstrate method robustness.