



From Leslyn Aaron, DBSQC/OCBQ
Tao Pan, DBSQC/OCBQ
Mark Levi, DBSQC/OCBQ
Alfred Del Grosso, DBSQC/OCBQ
Lokesh Bhattacharyya, DBSQC/OCBQ

To STN: #125590/0

Through William M. McCormick, Director, DBSQC/OCBQ

Product Human immunoglobulin (10%), RI-002

Sponsor ADMA Biologics, Inc.

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

Summary of Review

The new BLA (STN#125590) was submitted for human immunoglobulin (10%), RI-002, by ADMA Biologics, Inc. This Primary Discipline Review memo provides review of the procedures and validations of the following methods used in lot release of the drug product,

- (b) (4)
- Purity by (b) (4)
- Protein Assay by (b) (4) Method
- Polysorbate 80 Assay
- Determination Particulate Matter

There are outstanding IRs for the (b) (4) assay and for the method Determination Particulate Matter. There are no outstanding issues with the other three assays, which can be approved as lot-release tests for this drug product.

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 .

Submitted Information Reviewed

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

- 125590\0 – 3.2.S.4.1 Specifications (drug substance)
- 125590\0 – 3.2.S.4.2 Analytical Procedures
 - Analytical Procedures- Protein by (b) (4)
- 125590\0 – 3.2.S.4.3 Validation of Analytical Procedures
- 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 – 3.2.P.5.2. Analytical Procedures
 - TM-10011, Rev. 9: (b) (4) Assay Test Method for Biotest Pharmaceuticals Immune Globulin Drug Product.
 - Analytical Procedures – (b) (4) Purity (QC2161) : Method Summary
 - QC2161-Rev. 11: Determination of Human IgG (b) (4) Purity in Aqueous Samples by (b) (4)
 - QC2100-Rev. 18: Determination of Total Protein Concentration
 - QC2255: Determination of Polysorbate 80 by (b) (4)
 - Analytical Procedures – Particulate Matter (STP0011) : Method Summary
 - STP0011: SOP Particulate Matter
- 125590\0 – 3.2.P.5.3 Validation of Analytical Procedures
 - Validation of Analytical Procedures
 - AMVR-20121022-01: Method Validation Final Report – Validation of the (b) (4) Assay Test Method for IVIG Drug Product.
 - VP-FR-0312: Method Validation Final Report – Determination of IgG (b) (4) Aqueous Samples Using (b) (4)
 - VP-FR-0312-1: Method Validation Final Report – Addendum Final Report for Determination of IgG (b) (4)
 - VP-FR-0312-4: Method Validation Final Report – Assay Reagent Stability Evaluation for Determination of Human IgG (b) (4) Purity in Aqueous Samples by (b) (4)
 - VP-FR-0312-5: Method Validation Final Report – Addendum to Determination of IgG (b) (4) Aqueous Samples Using (b) (4)
 - Validation of Analytical Procedures- Protein
 - VP-FR-0156: Method Validation Final Report - Determination of Total Protein Concentration Using the (b) (4) Method

- VP-PQ-0156: Validation Protocol - Determination of Total Protein Concentration Using the (b) (4) Method
- VP-FR-0156-6: Addendum to Method Validation for Determination of Total Protein Concentration in the Range of (b) (4) Method
- Validation of Analytical Procedures - Polysorbate 80
- VP-FR-0541 - Method Validation Final Report - Polysorbate 80 Assay by (b) (4)
- VP-FR-0541-6 – Assay Reagent Stability Evaluation for Determination of Polysorbate 80 by (b) (4)
- 3.2.P.5.3.12 Validation of Analytical Procedures Particulate Matter
- 125590\0.12 – Quality Information Amendment – received 23 Nov 2015
 - 1.11.1 Response to FDA Request for Analytical Method Information (dated 09 Nov 2015)
 - TM-10011, Rev. 10: (b) (4) Assay Test Method for Biotest Pharmaceuticals Immune Globulin Drug Product.
 - AMVR-20121022-02: Method Validation Report – Validation of the (b) (4) Assay Test Method for IVIG Drug Product.
 - Report 20130816-1: Identification and Qualification of an Initial ALC for IVIG (b) (4) Assay
 - VP-PQ-0156: Addendum Validation Protocol - Determination of Total Protein Concentration Using the (b) (4) Method
 - #021 – 2 – (b) (4) Qualification Executive Summary
 - E041-4 – (b) (4) Requalification Executive Summary
 - 3.2.P.5.3.12 Validation of Analytical Procedures Particulate Matter
- 125590\0.19 – Quality Information Amendment – received 27 Jan 2016
 - 1.11.1 Response to FDA Request for Analytical Method Information (dated 15 Jan 2015)
 - TEC-16-003-RPT: Technical Report – Linearity of IgG (b) (4) Analyzed by Biotest SOP QC2161
 - SOP QC2110: Routine Operation and Maintenance of the (b) (4) System
- 125590\0.21 – Quality Information Amendment – received 29 Jan 2016
 - 1.11.1 FDA Request for Information (dated 08 Jan, 2016)
 - Report 20150624-1 Requalification of the Alert Level Control for IGIV (b) (4) Assay

Review Narrative

1. (b) (4) Assay

Method

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Conclusion


The method has been described clearly and the results for the evaluation of validation characteristics are acceptable. However, there are outstanding IRs.

2. Purity by (b) (4)

The method is described in SOP # QC2161, which is included in the submission. The release specifications for the drug product are: (b) (4)

Method





(b) (4)







Method Validation

The method provides relative quantitation of the active components, (b) (4), and that of the impurities, (b) (4), in one assay. The method validation report (VP-FR-0312) describes evaluation of linearity, precision (repeatability), specificity, LOQ, robustness and stability (b) (4) test).

(b) (4)



(b) (4)




Information Request and Review

The following information request was sent to the sponsor on 15 January 2016. The response was received as Amendment 19 on 27 January 2016.

1. With reference to SOP No. QC2161: Determination of Human IgG (b) (4) Purity in Aqueous Samples by (b) (4),
 - a. Please provide the details of the sample identified by the Sample Name “Test” in Attachment 1 (page 10) of your SOP

Review of the Response: The sponsor informed that the sample identified as “Test” is the system suitability standard, which is composed of the reference standard (a qualified lot of the drug product) in (b) (4) solution. As directed in Section 7.6.5 of SOP QC2161, it is run to observe the equipment performance by (b) (4)



- b. There is no mention of (b) (4) in your SOP No. QC2161. Please confirm that a (b) (4) can be used without (b) (4).

Review of the Response: The sponsor confirmed that a new (b) (4) does not require (b) (4). However, as indicated in the SOP sections 7.2 and 7.3 of SOP QC2110, the system needs to be (b) (4) until the base-line is stabilized. The cited SOP is included in Amendment 19.

2. Regarding validation of the (b) (4) Purity by (b) (4) assay method,

- a. You have determined concentrations of (b) (4) of a particular component and then plotted such concentrations against respective (b) (4) to demonstrate linearity of your method. You have determined (b) (4) of each component by (b) (4) which is constant at a particular protein concentration. Thus, you obtained the concentration of each component by (b) (4) by a constant. Hence, this is circular. Please provide plots of (b) (4) of each component against the total protein concentration of the drug product to demonstrate linearity of your method for each of the above components. Also, please provide correlation coefficient, slope, y-intercept and distribution of residuals for each plot.

Review of the Response: The sponsor provided Technical Report (TEC-16-003-RPT) (b) (4) are plotted against total protein concentration for (b) (4) in the concentration range (b) (4). The results show excellent linearity with correlation coefficients (b) (4) in all cases. The report also shows the linear regression plots, which show that the residuals are negligibly small and are essentially evenly distributed around 0, indicating no bias in the distribution of residuals.

- b. The (b) (4) are impurities present in your drug product. Please provide results to establish limits of quantitation (LOQ) of these components by your assay.

Review of the Response: LOQ was estimated to be (b) (4) for (b) (4), respectively, using the linearity data and following the method described in section 6.1 of ICH Q2(R1).

- c. Please provide composition of the (b) (4) and provide its (b) (4) obtained by your assay method to demonstrate that it does not have any (b) (4) that (b) (4) with any of the (b) (4) of (b) (4) to demonstrate specificity of your method.

Review of the Response: The sponsor provided composition of (b) (4) which contains glycine, chloride, and polysorbate 80, none of which is expected to (b) (4). The sponsor also informed that a (b) (4) obtained by the assay method is not available and indicated that the specificity described in section 5.3 of VP-FR-0312-5 demonstrates the quotient of the (b) (4).

and the (b) (4) in NaCl ranges from (b) (4) . As such, this is not complete response, however, based on (a) composition of (b) (4) , and (b) the residual plot included with the linearity study in response to question 2a above, which shows that the residuals are evenly distributed around 0, hence absence of residual bias, it is concluded that the sponsor has provided adequate information showing that (b) (4) cannot have any (b) (4) that (b) (4) with the (b) (4) in the drug product.

Conclusion

Based on the information provided in the original submission and Amendment 19, it is concluded that the method is described and validated adequately and can be approvable for the lot release testing of the drug product.

3. Protein Assay by (b) (4) Method

The (b) (4) is not further formulated to obtain the drug product but only filled into the final container. The specification for protein content for (b) (4) the drug product is between (b) (4)

Method:

The total protein content of the drug product is determined (b) (4)

This method was described in details in SOP QC2100 Rev.18, with information on the preparation of samples, standards and solutions, the execution of the analytical procedures, assay validity criteria, and the generation of reportable result. The description in the BLA submission is clear and adequate.

Method Validation

This method was validated as a quantitative assay for final drug product. The validation data were summarized in validation report VP-FR-0156, and the characteristics evaluated include linearity/range, precision (repeatability, intermediate precision), specificity, limit of detection (LOD), limit of Quantitation (LOQ), and robustness.

In report VP-FR-0156, the linearity of the method was verified by (b) (4)

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

In the original submission (VP-FR-0156), the (b) (4) method was intended to be validated as a quantitative assay for drug product (b) (4). The description of the testing procedures is adequate; the selection of validation characteristics was appropriate; and the robustness of the method was evaluated. However, the validation of the method's linearity, repeatability, LOD, LOQ, and range were not performed with the drug product. In addition, the accuracy was not validated and the experimental design for intermediate precision and specificity needs clarification. IR was submitted to seek further information.

Information Request and Review:

IR questions concerning this method were sent on November 9, 2015, and the sponsor responded in Amendment 12 on November 23, 2015.

- a. You have provided the validation report (VP-FR-0156) but not the validation protocol. We are unable to understand and review some of the validation data without the validation protocol. Please provide the validation protocol..

ADMA Response: Please find attached the validation protocol VP-PQ-0156 for report VP-FR-0156. Additionally, ADMA provided VP-PQ-0156-6 as it is a validation addendum protocol for (b) (4) and 10% IGIV which are reported in VP-FR-0156-6. Studies of 10% IGIV in (b) (4) are representative of RI-002.

Review of the response: The response is adequate, VP-PQ-156, VP-PQ-156-6, and FR-0156-6 were reviewed.

- b. You have not evaluated accuracy of the assay. Please provide data on accuracy of the method using the drug product.

ADMA Response: Accuracy of 10% IGIV in (b) (4), which is representative of RI-002, is reported in VP-FR-0156-6 and summarized in 3.2.P.5.3.21.3 under subheading VP-FR-0156-6. Accuracy was determined using Human IgG spiked into the (b) (4) of the Drug Product and assessed at (b) (4). Percent recovery from theoretical IgG concentration ranged from (b) (4).

Review of the response: Accuracy of 10% IGIV in (b) (4), which is representative of RI-002, is reported in VP-FR-0156-6 and summarized in 3.2.P.5.3.21.3 under subheading VP-FR-0156-6. (b) (4)

(b) (4) to represent drug products of protein concentrations of (b) (4). The protein concentrations of the above samples were measured with (b) (4) method and compared to the expected values. The %Recoveries at (b) (4), respectively, and the acceptance criterion, %Recovery between (b) (4) was met (FR-0156-6). The accuracy of the method has been validated in drug product matrix, and the response from the sponsor is adequate.

- c. It is unclear whether the linearity, precision, LOQ, and LOD were evaluated using

the drug product or standards. Please clarify. If these validation characteristics were not evaluated using the drug product, please provide data on linearity, precision, LOQ, and LOD of your method using the drug product.

Review of the response: In the validation report VP-FR-156-6, the linearity of the method was verified by (b) (4)



- d. You have evaluated intermediate precision of the assay with inter-analyst difference of two analysts, but you have not evaluated inter-day variation. Please provide data on inter-day variation of the assay.

Review of the response: This IR question has been adequately addressed in the addendum to the validation report VP-FR-156-6 in response to IR question c, as discussed above.

- e. It is unclear how the specificity of the assay was validated. If the study design involves diluting the sample with a certain buffer, and measuring the sample's concentration against standards diluted in the same buffer, then the effect of buffer matrices on specificity was not sufficiently addressed. Please provide adequate data to show that there is no effect of the buffer matrix on the assay results to demonstrate specificity of the assay.

Review of the response: In report VP-FR-0156-6, the specificity of the method was demonstrated by analyzing and comparing samples dissolved in (b) (4) and (b) (4) Human IgG dissolved into (b) (4) were measured and the results from the solution in (b) (4) was compared to that in (b) (4) The ratio of the protein concentration results in (b) (4) to IgG in

(b) (4), and met the acceptance criterion of between (b) (4). The drug product matrix ((b) (4)) was shown not to interfere with the test result, and the specificity of the method was validated. The reviewer found the response in the Amendment 0.12 is adequate.

- f. Please state the assay range clearly and provide experimental data that verify the range.

Review of the response: In report VP-FR-0156-6, the accuracy, precision, and linearity of the method have been established between the range of (b) (4). Therefore, it is acceptable to establish the working range of the method as (b) (4). The response in the Amendment 12 is adequate.

Conclusion

Based on the information provided in the original submission and Amendment 12, it is concluded that the accuracy, precision, linearity, specificity, range, LOQ, and robustness of the (b) (4) method has been validated, and the (b) (4) method is approvable for the lot release testing of RI-002 drug product.

4. Polysorbate 80 Assay

The quantity of Polysorbate 80, an excipient in the drug product is determined by derivatization of a polysorbate 80-(b) (4) complex using a standard curve generated with a Polysorbate 80 standard. The specification of (b) (4) was established based on the formulation of the product. The Analytical Procedure (QC2255) for the test method is included in the submission.

Method

The samples are (b) (4)







Method Validation

The following characteristics were studied to validate the method: specificity, linearity, accuracy, intermediate precision, solution stability, range, robustness, LOD, and LOQ.

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

(b) (4)



Conclusion

Suitability of the Polysorbate 80 procedure has been satisfactorily demonstrated for assay of Drug Product samples.

5. Determination Particulate Matter

Determination of particulate matter is performed by a (b) (4) test according to (b) (4) In this technique, (b) (4)



Method

ADMA provided a method summary along with a detailed SOP (STP0011) from (b) (4)



(b) (4)

Information Request and Review

IR questions concerning this method were sent on November 9, 2015, and the sponsor responded in Amendment 12 on November 23, 2015.

- a. Regarding the Test for Particulate Matter (STP-0011), you have indicated in 3.2.P.5 Section 3.12 that the “test is performed per compendial method, (b) (4) ... a complete validation is not necessary.” Please submit information that this procedure has been verified for suitability under conditions of use. At a minimum, please submit data for repeatability and intermediate precision obtained for the RI-002 Injection, Sterile solution.

Review of the response: ADMA responded that (b) (4) has been inspected by the FDA and have performed the (b) (4) test for Particulate Matter (b) (4) in support of BLAs and NDAs, and performs the assay for routine release of pharmaceuticals.

(b) (4)

Two Executive Summary documents are included as examples of equipment qualification. (E041-2 (b) (4) Qualification Executive Summary and E041-4 (b) (4) Requalification Executive Summary). Section 3.2.P.5.3.12 has been revised to reflect the qualification and calibration activities.

The submitted qualification reports were reviewed and observed to have met the stated acceptance criteria for the (b) (4). The revision of 3.2.P.5.3.12 was observed to be a restatement of the acceptance criteria for precision and accuracy of the particle size standards used in the instrument calibration. Data regarding repeatability and

intermediate precision of RI-002 Injection samples, as requested in the November 9 IR, was not included.

At this time the following additional information request has been submitted in response to ADMA's initial response, and is pending submission to the sponsor:

- 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 this information.

Conclusion

The method for Particulate Matter is consistent with (b) (4) and is an appropriate method for the intended purpose of quantitating particulate contamination with respect to the specification limits. Suitability under conditions of use and performance of the procedure for the specific RI-002 product still needs to be demonstrated.