



**MEMORANDUM**

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**To** STN 125596/0

**Through** William M. McCormick, Director DBSQC/OCBQ

**Sponsor** Baxalta

**Product** Immune Globulin Subcutaneous (Human), 20% Solution (CUVITRU®)

**Subject** Primary Review Memo for the Method Validation for the Quality Control Release Tests for the Drug Product, STN: 125596

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**Summary**

A new BLA was submitted by Baxalta for CUVITRU, an Immune Globulin, 20% solution to be administered subcutaneously for the treatments of primary immune deficiency disorders associated with defects in humoral immunity which include but are not limited to congenital X-linked agammaglobulinemia, common variable immune deficiency, Wiskott-Aldrich syndrome, and severe combined immune deficiencies. This document constitutes the Primary Review Memo from DBSQC for the following analytical methods and their validations, which are proposed to be used for quality control lot release of the drug product.

1. TnBP, Tween 80 and Triton X-100 quantification by (b) (4) (Primary Method)
2. TnBP by (b) (4) (Alternate method)
3. Total Protein by (b) (4) (Alternate method)
4. Polysorbate 80 by (b) (4) (Alternate method)
5. pH Assay
6. (b) (4)
7. Purity by (b) (4)
8. Total Protein by (b) (4)
9. Glycine by (b) (4)

## 10. Octoxynol 9 by (b) (4)

Review of the methods and their validations led to 8 Information Requests (IR), which were submitted on 30 September 2015, 30 November 2015 and 4 December 2015, 20 January 2016, 10 February 2016, 20 January 2016, 3 May 2016, and 13 May 2016. The sponsor provided responses to the IRs on 14 October 2015, 11 December 2015 (covering both 30 November and 4 December RFIs), 3 February 2016, 26 February 2016, and 30 March 2016 as Amendments 1, 4, 5, 7, and 16, respectively, and two draft responses on 12 May 2016 and 22 June 2016.

Conclusion: Eight of the methods, method number 1-6 and 8-9 listed above, used for lot release of the drug product are adequately described and validated for the intended use. However, there are outstanding issues for method validation of the method number 7 “Purity by (b) (4)” assay. The method “Octoxynol 9 by (b) (4)” (method number 10 above) was withdrawn from the submission in the amendment 5 dated Feb. 3, 2016.

## Background

Immunoglobulin is obtained from donated human plasma which is processed, purified, and is supplied as a liquid solution. IGSC, 20% is essentially the same as Baxter’s GAMMAGARD LIQUID IGI, 10% product (STN 125105). The only differences are (b) (4) and formulation steps. The product is formulated in single-dose vials at 5ml/1g, 10ml/2g, 20ml/4g, and 40ml/8g.

## Submitted Information and Documents

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

125596/0.0

- 3.2.P.5.1 Control of Drug Product –Specifications US
- 3.2.P.5.2 Control of Drug Product – Analytical Procedures
- CTP LE-13-A22001-CTP00 Glycine quantification by (b) (4)
- CTP LE-13-A01001-CTP00 Quantitation of TNBP by (b) (4)
- CTP LE-13-A21008-CTP00 Determination of Tween 80/Polysorbate80 by (b) (4)
- CTP LE-13-A21002-CTP00 Total protein quantification by (b) (4)
- CTP LE-13-A26002-CTP00 Total protein quantification by (b) (4)
- CTP LE-13-A03008-CTP00 TNBP, Tween, and Triton Quantification by (b) (4) and Final Container Gammagard S/D, Gammagard liquid/Kiovig and IGSC, 20% (SUBQ20%) Samples
- CTP LE-13-A04001-CTP00 (b) (4) of Gammagard S/D, Gammagard liquid/Kiovig and IGSC, 20% products by (b) (4)

- CTP LE-13-A05001-CTP00 Purity determination and (b) (4) quantification in IVIG products by (b) (4)
- CTP LE-13-A29001-CTP00 pH determination
  - 3.2.P.5.3 Control of Drug Product – Validation of Analytical Procedures
- Doc. LE-65-A04001S/01 (b) (4) on IGSC 20%
- Doc. LE-65-A29001S/01 pH
- Doc. LE-65-A03008S/01 TnBP, Tween and Triton quantification by (b) (4) in Final Container IGSC 20%
- Doc. LE-65-A21008S/01 Determination of Tween-80 on IGSC 20%
- Doc. LE-65-A05001S/02, Purity determination by (b) (4) PV-LA-13.032/0.0 & 1.0<sup>(b) (4)</sup>
- Doc. LE-65-A26002S/01 Total protein determination using (b) (4) on Sub Q20%
- Doc. LE-65-A21002S/02 Assay of total protein, (b) (4) Method on IGSC 20%
- Doc. LE-65-A01001S/01 Quantitation of Tri-(n-Butyl) Phosphate by (b) (4) on IGSC 20%
- Doc. LE-65-A22001S/01-VR & PV-LA-08-032-VP Glycine quantitation by (b) (4) on Sub Q20%
- 3.2.P.5.4 Batch Analyses

## 125596/0.1

- 1.11.1 Response to Question 1 Dated 30 Sep 2015
- 3.2.P.5.3 Control of Drug Product – Validation of Analytical Procedures
- PV-LA-14.012/0.0 Validation of Triton X-100 for IGSC,
- PV-LA-14.012/0.1 Validation of Triton X-100 for IGSC, Amendment 1
- PV-LA-13.032/0.0 Validation of purity determination in IGSC 20% by (b) (4)
- PV-LA-09.007 Validation of the (b) (4) current compendial procedure for the testing of Gammagard liquid 20% (SubQ 20%)
- PV-LA-08.033/0.0 Validation of the Total protein determination by (b) (4) method on Gammagard liquid 20% Sub Q20%
- PV-LA-08-032/1.0 Validation in terms of accuracy, precision, linearity, range and specificity of the glycine quantitation by (b) (4) (control test procedure LE-13-A22001) on 20% Gammagard liquid

## 125596/0.4

- 1.11.1 Response to RFIs dated 30 November and 4 December 2015; response received on 11 December 2015

## 125596/0.5

- 1.11.1 Response to FDA RFI dated 20 January 2016; response received on 4 February 2016
- 3.2.P.5.2 Control of Drug Product – Analytical Procedures

- CTP LE-13-A05001/12 Purity determination and (b) (4) quantification in IVIG products by (b) (4)

125596/0.7

- RFI dated 10 February 2016 response received on 26 February 2016
- 3.2.P.5.2 Analytical Procedures
- LE-13-A04001/12 (b) (4) of Gammagard S/D, Gammagard liquid/Kiovig and IGSC 20% products by (b) (4)

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- 1.11.1 Quality Information Amendment for Committed Reports dated 20 January 2016; response received on 30 March 2016
- 3.2.P.5.2 Control of Drug Product – Analytical Procedures
- CTP LE-13-A26002/15 Total protein quantification in accordance with the (b) (4) method
- 3.2.P.5.3 Control of Drug Product – Validation of Analytical Procedures
- FR PV-LA-16.001 Validation of the (b) (4) current compendial procedure for the testing of IGSC 20%: complement for linearity and limit of quantification.
- PV-LA-16.002 Validation addendum of the total protein determination by (b) (4) method for the testing on IGSC 20%
- PV-LA-16.004 (b) (4) current compendial procedure for the testing of IGSC 20%: complement of validation for accuracy
- Draft responses to Request for Information Dated 2016-MAY-03, e-mails from Aderonke Denloye to Thomas Maruna dated 12 May, 2016 and 22 June, 2016

## Review Narrative

### 1. TnBP, Tween 80 and Triton X-100 quantification by (b) (4) (Primary Method)

This method is used for quantitating TnBP, Tween, and Triton (TTT) (b) (4) and final container Gammagard S/D (5% IVIG), Gammagard liquid/Kiovig (10% IVIG) and IGSC 20% (SubQ20%). The sponsor provided a Control Test Procedure, LE-13-A03008-CTP00, as well as a validation report, LE-65-A03008S/02. The release specifications for the IGSC, 20% drug product (DP) are TnBP not more than (b) (4), Triton X-100 (b) (4), and Tween 80 (b) (4).

#### Method

(b) (4)

(b) (4) [Redacted]

[Redacted]

[Redacted]

| [Redacted]

| [Redacted]

[Redacted]

| [Redacted]

| [Redacted]

| [Redacted]

| [Redacted]

| [Redacted]

The method is adequately described in the SOP.

Method Validation

The following characteristics were studied to validate the method: selectivity (specificity), repeatability, intermediate precision, linearity, accuracy, LOD, LOQ, and range.

(b) (4) [Redacted]

2 pages have been determined to be not releasable: (b)(4)

(b) (4) [Redacted text block containing multiple lines of obscured content]

Information Request and Review

The following IR was submitted to the sponsor on 30 September 2015. The responses were received on 14 October 2015 as Amendment 1. The IR question, the response of the sponsor and review of the responses are discussed below

In Table 5 on pages 6 and 7 of the validation report (LE-65-A03008S/02), in the columns for Repeatability and Intermediate Precision, please correct what appears to be a typographical error in the data for TnBP, Triton X-100, and Tween80. In Table 5 on pages 6 and 7, in the columns for Repeatability and Intermediate Precision, please correct what appears to be a typographical error in the data for TnBP, Triton X-100, and Tween80. Part of the table is shown below to illustrate the error.

Review of Response: A corrected validation report (LE-65-A03008S/02) was submitted correcting the typographical error. This was acceptable

Conclusion: This method has been adequately validated.

**2. TnBP by (b) (4) (Alternate method)**

The release specifications of TnBP for the IGSC, 20% DP) is (b) (4) .

Method

(b) (4)

A large rectangular area of the page is completely redacted with a solid grey fill. The redaction covers the entire body of the document, starting below the 'Method' header and ending above the final paragraph. The only visible text within this redacted area is the label '(b) (4)' at the top left.

The method is adequately described in the SOP (LE-13-A01001-CTP00).



(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

The method is adequately described in the SOP (LE-13-A21002-CTP00).

Method Validation

(b) (4) [Redacted]

[Redacted]

[Redacted]



Method Validation

[Redacted text block containing multiple paragraphs of information, likely a table or detailed description of the validation process.]

Conclusion: The method was adequately validated.

**5. pH Assay**

The release specification for pH is 4.6 – 5.1 for the IGSC, 20% DP.

Method

The pH of the drug product (DP) sample is measured by (b) (4) [Redacted]

Method Validation

(b) (4) [Redacted]

**Conclusion:** The method is reasonably validated for the intended pH measurement. This being a compendial method, assessment of other characteristics is not necessary.

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)



Information requests (IR) and Reviews

The following IRs were sent to the sponsor regarding the (b) (4) method and validation report on Nov. 16, 2015. The partial response was partially received on Dec. 11, 2015 in amendment 4.

1. Method (LE-13-A04001)

- Please confirm that (b) (4) is used for the IGSC 20% sample before (b) (4) in section 4.2
- Please specify the (b) (4)
- Please specify the (b) (4)
- Please provide details of buffer composition, concentration and pH values for the storage buffer in section 3.4

Review of the response:

In the response, the sponsor clarified:

(b) (4) is used for the IGSC 20% sample;

(b) (4)

(b) (4)

(b) (4)

The SOP CTP was updated to include all above details (Version 12) in amendment 7 dated Feb. 26, 2016. The responses are acceptable.

2. Validation report (Doc ID: LE-65-A4001S/01 and PV-LA-09.007)

(b) (4)

Review of the response:

The sponsor agreed to perform a full validation for this method in the response and outlined the plan for the evaluation of linearity, accuracy, precision, specificity and LOQ in the response and estimated that it would be completed by the end of Feb. 2016. FDA reviewer did not agree with the proposed accuracy study and instructed that “The accuracy of this assay can be determined by performing spike-recovery study with a (b) (4) IgG sample.”

The second IR regarding the precision evaluation and re-validation design was sent to the sponsor on Jan. 20, 2016. The response was received on Feb. 05, 2016 in amendment 05.

- a. The precision evaluation for the method was submitted PV-LA- 09.007 in amendment 01 (dated Oct. 14, 2015). Three out of (b) (4) results (Table 5) failed to meet the set acceptance criteria. Please explain why the precision study can be considered satisfactory.
- b. For the submitted re-validation procedure dated Dec. 11, 2015. We don't agree with your accuracy study proposal. (b) (4) requirement doesn't address the accuracy but the specificity. The accuracy of this assay can be determined by performing spike-recovery study with a (b) (4) IgG sample.

Review of the response

- a. The sponsor thought that precision data was acceptable because results for the samples were within specification limits. FDA reviewer disagreed with such conclusion because the precision and accuracy are two different aspects of an assay evaluation and both of them need to meet the set acceptance criteria for the intended use. The response is not acceptable.
- b. The sponsor agreed to perform the accuracy study with spike-recovery procedure. The submission date of validation report was estimated by March 31, 2016. The response is acceptable.

After review of the completed validation report submitted by the sponsor on Feb. 3 2016 as amendment 5 and March 30, 2016 as amendment 16, the third IR was sent to the sponsor on May 03, 2016. A draft response was received on May 12, 2016.

1. You have not provided acceptable response to our question 1a in amendment 5. That your results met specification, do not justify that your results did not have to meet your internal acceptance criteria for precision (repeatability and intermediate precision). Based on your results, we feel that your validation studies failed to demonstrate adequate repeatability and intermediate precision of the assay. Please explain why your results did not meet your internal acceptance criteria and provide data to show that your results could meet your internal acceptance criteria consistently.

Review of the response

The sponsor realized the RSD acceptance criteria of (b) (4) for repeatability and (b) (4) for intermediate precision for all components set previously for precision study were reasonable only for (b) (4). They are too low for the impurity components of this DP because (b) (4)

Thus the RSD are adjusted to (b) (4) for repeatability and (b) (4) for intermediate precision for (b) (4). With this adjustment, all results meet the acceptance criteria. The revised acceptance criteria are acceptable.

2. You determined LOQ by (b) (4) in the report PV-LA-16.001. We do not agree with your method for the determination of LOQ. In addition, it is not clear to us what (b) (4) means because (b) (4). LOQ should be determined separately for (b) (4)

(b) (4). Additionally, LOQ should be expressed in terms of reportable result, which is (b) (4) for this assay. Alternatively, LOQ may be determined by (b) (4) and using the equation  $LOQ = 10\sigma/S$  as described in ICH Q2(R1). Please reevaluate the LOQ and submit results for review.

#### Review of the response

The LOQ determination for (b) (4) in the response is considered inappropriate. A follow-up IR was sent to the sponsor on May 13, 2016 regarding this issue as following. The sponsor revised the draft response and submitted a revised draft response on June 22, 2016.

For this assay, LOQ is required for (b) (4). We disagree with your LOQ determination for (b) (4) in response to the question 2. In the table 5, you found that a sample with (b) (4). Thus you calculated that the LOQ for (b) (4). The LOQ of (b) (4) is calculated using a similar approach. Please provide your justification or a scientific reference article for such approach for the LOQ determination in a (b) (4) method.

If you conclude that LOQ for (b) (4) respectively, please provide data in support of your conclusion from samples, which contain (b) (4), respectively. The data should show adequate accuracy, precision, and (b) (4).

The figure 4 in your response is not adequate. Using ICH Q2(R1) equation  $LOQ = 10\sigma/S$  to determine the LOQ (b) (4) assay, multiple points are required for (b) (4) below your specification limit. Please provide adequate data to establish LOQ of your assay for both impurities.

In the revised draft response (dated June 22, 2016), the sponsor stated they cannot find an appropriate plot for LOQ calculation (b) (4)

(b) (4). LOQs were determined actually determined based on accuracy, precision,

3. You performed (b) (4) of spiking experiment using a (b) (4) IGSC 20% sample on a normal IGSC 20% sample for accuracy study in the validation report PV-LA-16.004. But the recoveries are not calculated and thus the results are inconclusive for the accuracy of the method. Please calculate the recoveries for (b) (4) and submit for review.

Review of the response

The requested recovery data are provided in the response. They are (b) (4)

[Redacted]

The response is acceptable.

Conclusion: The (b) (4) method is adequately validated for the intended use.

**7. Purity by (b) (4)**

Purity is determined by (b) (4) sample. The specification for the DP is no less than 98%.

Method

(b) (4)

Method Validation

(b) (4)

(b) (4)

#### Information requests (IR) and Review

The following IRs were sent to the sponsor on Jan. 20, 2016 regarding the method. The responses were received on Feb. 3, 2016 (amendment 5).

1. Please include a typical (b) (4) of IGSC 20% DP sample in the CTP.

Review of the response: A revised CTP (version 12) was submitted which included (b) (4) of (b) (4) and IGSC 20% final product. The response is satisfactory.

2. Please provide sample preparation details, including (b) (4) for IGSC 20% DP samples injected for (b) (4) in the CTP. Also, please revise your CTP to include (b) (4) conditions such as (b) (4) resubmit for review.

Review of the response: Requested details were added to the new version of the CTP. The response is satisfactory.

The information request for a full validation was sent on July 20, 2016 and the response is pending.

For “Purity by (b) (4)” assay (CTP LE-13-A05001), you have demonstrated the specificity and precision in your validation report. Please provide accuracy, linearity, and range data to complete a full validation for this quantitative method.

Conclusion: The validation is not adequate for the intended use as a quantitative test for IGSC 20% DP. A full validation has been requested. As of the time of writing this memo, we have not received response from the sponsor.

#### **8. Total Protein by (b) (4) Method**

A (b) (4) method is used for the determination of the total protein in the DP sample. The protein specification for this DP is (b) (4).

#### Method

(b) (4)

(b) (4)



Method Validation

The quantitative method is evaluated by the performance characteristics of specificity, accuracy, precision, linearity, range and Limit of Quantitation (LOQ).

(b) (4)



(b) (4)

Information request (IR) and Review

The following IR was sent to the sponsor on Jan. 20, 2016 regarding the method and validation report. The response was received on Mar. 30, 2016 (amendment 16) with supporting data.

As evaluated in the validation report (PV-LA06.022), the LOQ of the assay is (b) (4). However, the (b) (4) IGSC 20% sample has a typical (b) (4) value of (b) (4) (page 4 of LE-65-A25002S), which is below the LOQ. Please revise the CTP (LE-13-A26002-CTP00) to (b) (4) the sample volume for the determination of (b) (4) of IGSC 20% DP to make sure that the (b) (4) value is above LOQ to obtain appropriate value of (b) (4) for calculation of (b) (4) in the sample.

Review of the response: The sponsor revised the SOP to (b) (4) of sample for the (b) (4) measurement in order to keep measured (b) (4) value above LOQ of the method. The RSD for repeatability and intermediate precision are within the acceptance criteria.

In addition, LOQ for (b) (4) amount was evaluated by (b) (4) [redacted]. This value is smaller than the LOQ for the (b) (4) measurement for this assay, which indicated that the (b) (4) from (b) (4) [redacted]. The response is satisfactory.

Conclusion: The method is adequately described and method validation is adequate for the intended use.

**9. Glycine by (b) (4)**

The specification for glycine for this DP is (b) (4) [redacted].

Method

(b) (4) [redacted]

Method Validation

(b) (4) [redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Information request (IR) and Review

The following IR was sent to the sponsor on Jan. 20, 2016 regarding the method and validation report. The response was received on Feb. 3, 2016 (amendment 5).

In the specificity section of the validation report (LE-65-A25002S), you stated that the [Redacted] (b) (4) [Redacted]. Please provide scientific literature reference(s) for this conclusion.

Review of the response: (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

The response is acceptable.

Conclusion: The method is adequately described and validated for the intended use.