



## MEMORANDUM

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CMC Reviewer  
Laboratory of Analytical Chemistry and Blood Related Products (LACBRP)  
Division of Biological Standards and Quality Control (DBSQC)  
Office of Compliance and Biologics Quality (OCBQ)  
Center for Biologics Evaluation and Research (CBER)  
Food and Drug Administration (FDA)

**To:** Biologics License Application Submission Tracking Number # 125587/0

**Subject:** Review of Analytical Procedures for Drug Product of Biologics License  
Application for PANZYGA® (NewGam 10%) Immune Globulin Intravenous,  
Human 10%

**Through:** Lokesh Bhattacharyya, Ph.D., Lab Chief, LACBRP/DBSQC/OCBQ/CBER  
William M. McCormick, Ph.D., Director, DBSQC/OCBQ/CBER

**Applicant:** Octapharma

**Product:** PANZYGA® (NewGam 10%) Immune Globulin Intravenous, Human 10%

**Biologics License Application (BLA) Submission Tracking Number (STN) #:** 125587

**Submission received by CBER:** April 15, 2015

**Review completed:** October 23, 2015

### Executive Summary:

After a thorough review of this BLA submission, this DBSQC reviewer finds that Octapharma's (b) (4) assay is adequately validated for the (b) (4) determination of Octagam final product by evaluating the method with characteristics of specificity, accuracy, precision, linearity, range and robustness. But whether the method is also validated for the final container (FC) of NewGam is still pending.

### Background

Panzyga® is indicated for the treatment of primary humoral immunodeficiency and chronic immune thrombocytopenic purpura in adults.

The FC of Panzyga® is composed of 10% active ingredient – human normal immunoglobulin G (IgG) for intravenous administration (IV). The proposed specifications for (b) (4) for IgG in FC are (b) (4), monomers and dimers  $\geq 90\%$  and fragments  $\leq 3\%$ .

DBSQC reviews BLA and related supplements to ensure analytical methods are adequately validated for the intended use.

### Documents Reviewed

#### Original submission

- Cover letter, dated April 15, 2015
- 3.2.P.5.3 Validation of Analytical Procedures: Master –SOP for analytical determination 130SOP071/03 “Determination of (b) (4) of Immunoglobulin by (b) (4)”
- 3.2.P.5.1 Final product specification
- 3.2.P.5.4 Batch analysis
- 3.2.P.5.3 Validation of Analytical Procedures: Analytical method validation report 000VAL071 FC 84x 85x IP 7xx/01 “Determination of (b) (4) of Immunoglobulin by (b) (4)”
- 3.2.P.5.3 Validation of Analytical Procedures: Analytical method validation report 000VAL071 FC 84x 85x IP 7xx/01 supplement 1 “Determination of (b) (4) of Immunoglobulin by (b) (4); Supplement 1: Change of Standard and Addition of NEWGAM®”

#### Amendment 05, received June 08, 2015

- Updated validation report 000VAL071 FC 84x 85x IP 7xx/01 “Determination of (b) (4) of Immunoglobulin by (b) (4)”

#### Amendment 07, received June 30, 2015

- Response to information request dated June 17, 2015
- Updated SOP 130SOP071/04 “Determination of (b) (4) of Immunoglobulin by (b) (4)”
- Updated validation report 000VAL071 FC 84x 85x IP 7xx/02 “Determination of (b) (4) of Immunoglobulin by (b) (4)”


Amendment 10, received July 27, 2015

- Response to information request dated July 16, 2015
- Updated SOP 130SOP071/05 “Determination of (b) (4) of Immunoglobulin by (b) (4)”
- Updated validation report 000VAL071 FC 84x 85x IP 7xx/03 “Determination of (b) (4) of Immunoglobulin by (b) (4)”

## Review Narrative

### Method

(b) (4)



### Validation

The method was validated as a quantitative method for the (b) (4) percentage of monomers and dimers (b) (4), and as a quantitative Impurity test for the (b) (4) percentages of (b) (4) as well as for (b) (4).

The specificity of the method is evaluated by (b) (4)

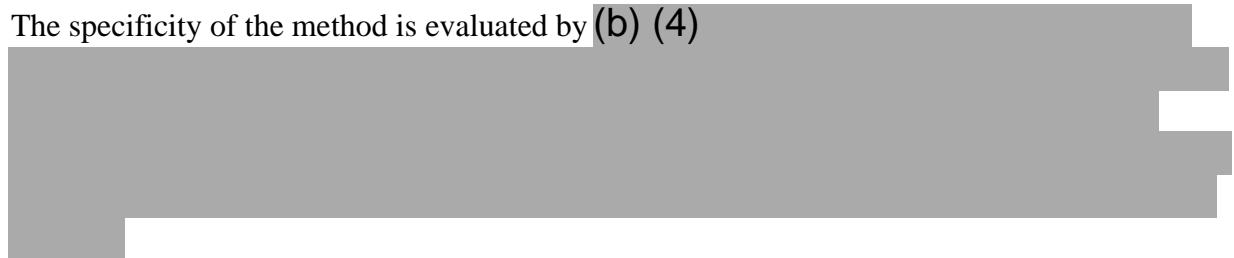


Table 1. Summary for specificity study

(b) (4)

Accuracy of percentage of monomers (b) (4)

(b) (4)

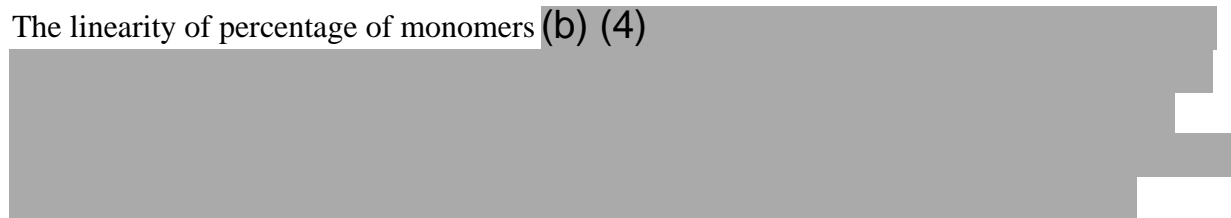
Accuracy of (b) (4)

(b) (4)

(b) (4)

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The linearity of percentage of monomers (b) (4)

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The linearity of (b) (4)

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The linearity of (b) (4)

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Repeatability was performed on both positive and negative controls. Both controls were prepared and analyzed <sup>(b) (4)</sup> times by the same analyst and the assay was performed on the same instrument on the same day. Intermediate precision was performed on <sup>(b) (4)</sup> days by <sup>(b) (4)</sup> different analysts using both controls. The results are summarized in Table 2.

(b) (4)

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(b) (4)

Limit of quantitation (LOQ) for (b) (4) percentages are determined by following formula:

(b) (4)

(b) (4)

The robustness is evaluated by (b) (4)

(b) (4)

#### Information Request (IR) and reviews

An IR was sent to the sponsor on June 05, 2015 because the pages of 82-91 of the validation report (000VAL071FC 84x 85x IP 7xx/01) "Report of the Method Validation for the

(b) (4) in Human Immunoglobulin by (b) (4)

(b) (4) ” could not be accessed by the reviewer. The response was received on June 08, 2015 and the updated validation report can be fully accessed.

The second IR was sent to the sponsor on June 17, 2015. The responses were received on June 30, 2015.

1. Please add the following details in the SOP and resubmit for review:
  - a. Your validation report shows that the samples should be analyzed within (b) (4) of preparation. Please update section 5.1 of your SOP to indicate that the samples should be analyzed within (b) (4) of preparation.
  - b. Please add the (b) (4) preparation procedure, storage condition and duration of use in section 5.
  - c. Describe (b) (4) in section 5.5.
  - d. Describe the (b) (4) parameters such as (b) (4) in section 6.1

#### Review of the response

The sponsor provided an updated SOP with the requested details of sample stable period, (b) (4) preparation and usage period, (b) (4). The response is satisfactory.

2. Please provide the following details in the validation report:
  - a. Please provide the acceptance criteria for recovery studies of (b) (4) percentages using (b) (4) in section 6.3.
  - b. Please provide the (b) (4) acceptance criterion for (b) (4) percentage using (b) (4) in section 6.3.
  - c. Provide repeatability and intermediate precision results of (b) (4) percentage for the negative control (b) (4) in section 6.4.
  - d. You have not reported the experiment data and acceptance criteria for Accuracy, Precision, Linearity, Range and Robustness study for the percentage of monomer plus (b) (4) in the validation report. Please provide the data for review.

#### Review of the response

The validation report was updated (000VAL071 FC 8xx IP 7xx/02). The acceptance criteria for recovery study of (b) (4) were both set at (b) (4). The linearity ranges for (b) (4) were reevaluated properly to be (b) (4) respectively based on these criteria. The (b) (4) acceptance criterion for (b) (4) percentage using (b) (4). In the response the sponsor stated that precision results of the (b) (4) percentage for the negative control (b) (4) were not presented in the original validation report because the values are below the LOQ (LOQ for

(b) (4). The validation results for accuracy, precision, linearity, range and robustness studies for the percentage of monomer plus (b) (4) were included in the updated validation report, which are summarized in above method validation section. The response and additional supporting data are satisfactory.

The third IR was sent to the sponsor on July 16, 2015. The responses were received on July 27, 2015 in amendment 10.

Please make following corrections in your SOP (130SOP071/04) and validation report (000VAL071 FC 8xx IP 7xx/02) for LOQ and range of (b) (4) percentage determination using (b) (4) and resubmit for review:

- Range is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy and precision. According to provided results, range for (b) (4) percentage should be (b) (4) instead of (b) (4).
- LOQ is the lowest amount of analyte in a sample which can be quantitatively determined with acceptable accuracy and precision. According to provided results, LOQ for (b) (4) percentage should be (b) (4) instead of (b) (4).

#### Review of the responses

The sponsor has reevaluated the validation report and confirmed that the lowest concentration with recoveries between (b) (4). Hence the LOQ for (b) (4) percentage is (b) (4) and the validated range is (b) (4). The SOP and the validation report are both updated accordingly. The response is satisfactory.

An additional IR was sent to the sponsor on October 23, 2015. The response is still pending at the time of writing this memo.

We noticed that the samples used in your validation report (000VAL071 FC 84x 85x IP 7XX/03) for this method are Octagam final products. Only the specificity was re-evaluated in the supplement report (000VAL071 FC 84x 85x IP 7xx/01 supplement 1) with Newgam samples. Please explain why the Newgam samples have equivalent outcome for validation characteristics of linearity, range, accuracy, precision, LOQ and robustness as the Octagam samples.

#### Conclusion

The decision whether this method is adequately validated for the (b) (4) determination of Newgam FC is pending.



