



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

MEMORANDUM

Date: July 10, 2019

To: Biologics License Application: STN# 125683/0

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Applicant: Grifols Therapeutics LLC

Product: Immune Globulin Subcutaneous (Human), 20% (IGSC 20%)

Submitted: July 9, 2018

Subject: Review of analytical methods and validations used for product identity and quality in Immune Globulin Subcutaneous (Human), 20% (IGSC 20%)

Recommendation: Approval

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Summary of Review

The original Biologics License Application (BLA) STN# 125683/0 for Immune Globulin Subcutaneous (Human), 20% (IGSC 20%, XEMBIFY), was submitted by Grifols Therapeutics LLC on July 09, 2018 for approval to treat primary immunodeficiency (PI) in patients 2 years of age and older. This Primary Review Memo evaluates the following analytical methods and their validations:

1. [\(b\) \(4\) for Plasma Products](#)
2. [Protein Profiling Using \(b\) \(4\)](#)
3. [Protein Determination by \(b\) \(4\) Method](#)
4. [Purity of Protein and Product Identity by \(b\) \(4\)](#)

Based on the review of the original submissions and amendments, the assays listed above are approvable for use in identity and quality control testing for Immune Globulin Subcutaneous (Human), 20% (IGSC 20%) drug product.

Background

Primary Immunodeficiency diseases (PIDs) are a family of congenital disorders of the immune system that lead to an increase in frequency of infections. Most PIDs cause the body to produce too few or no immunoglobulins. Immunoglobulin replacement is the most important treatment for these PIDs, as it helps to protect against a range of infections and to reduce autoimmune symptoms.

Immune Globulin Subcutaneous (Human), 20% (IGSC 20%, XEMBIFY) is a solution of purified human immunoglobulin made from large pools of human plasma with total protein concentration of 18-22%. The main component of IGSC 20% is gamma immunoglobulin (IgG), which is identified by (b) (4). Immunoglobulin A is quantified by (b) (4). The protein concentration is detected by (b) (4) Method, and protein composition is determined by (b) (4).

Submitted Information Reviewed

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

(1). 125683/0

3.2.P.5.2 – Analytical Procedures

- CS-000-BC-041 (b) (4) for Plasma Products
- CS-000BF-036 Protein Profiling Using (b) (4)
- CS-000-BC-052 Protein Determination by (b) (4) Method
- CS-000-BC-2000 Purity of Protein and Product Identity by (b) (4)

(2). 125683/0

3.2.P.5.3 – Validation of Analytical Procedures

- BA-RVAL-000006 Validation of (b) (4) Method for 20% IGSC
- QOAS-2015-068 Validation of Protein Profiling Using (b) (4) 20% IGSC (b) (4)
- QOAS-2015-001 Validation of Protein Determination by (b) (4) Method
- QOAS-2014-083 Validation of CS-000-BC-200, Purity of protein and Product Identity by (b) (4)

(3). 125683/0.10- Quality Information Amendment


Review

1. (b) (4) for Plasma Products

Method

(b) (4)

(b) (4)

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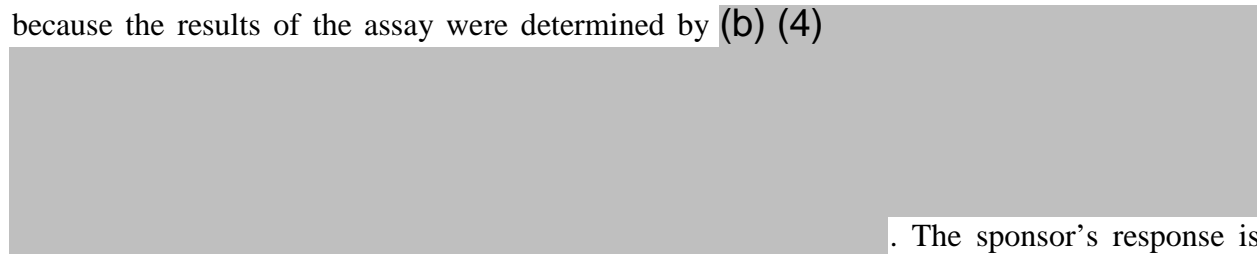
The response filed as Amendment 125683/0.10, was received on November 2, 2018. The IR questions and review of the responses are discussed below.

Information Request and Reviews

Please provide the detail validation report, including image data for validation of the test method CS-000-BC-041 (b) (4) of Plasma Products).

IR response review

The sponsor explained more detail was not provided in validation report BA-RVAL-000006 because the results of the assay were determined by (b) (4)

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. The sponsor's response is acceptable.

Conclusions

(b) (4) Method for 20% IGSC was validated and the validation acceptance criteria were fulfilled for specificity.

2. Protein Profiling Using (b) (4)

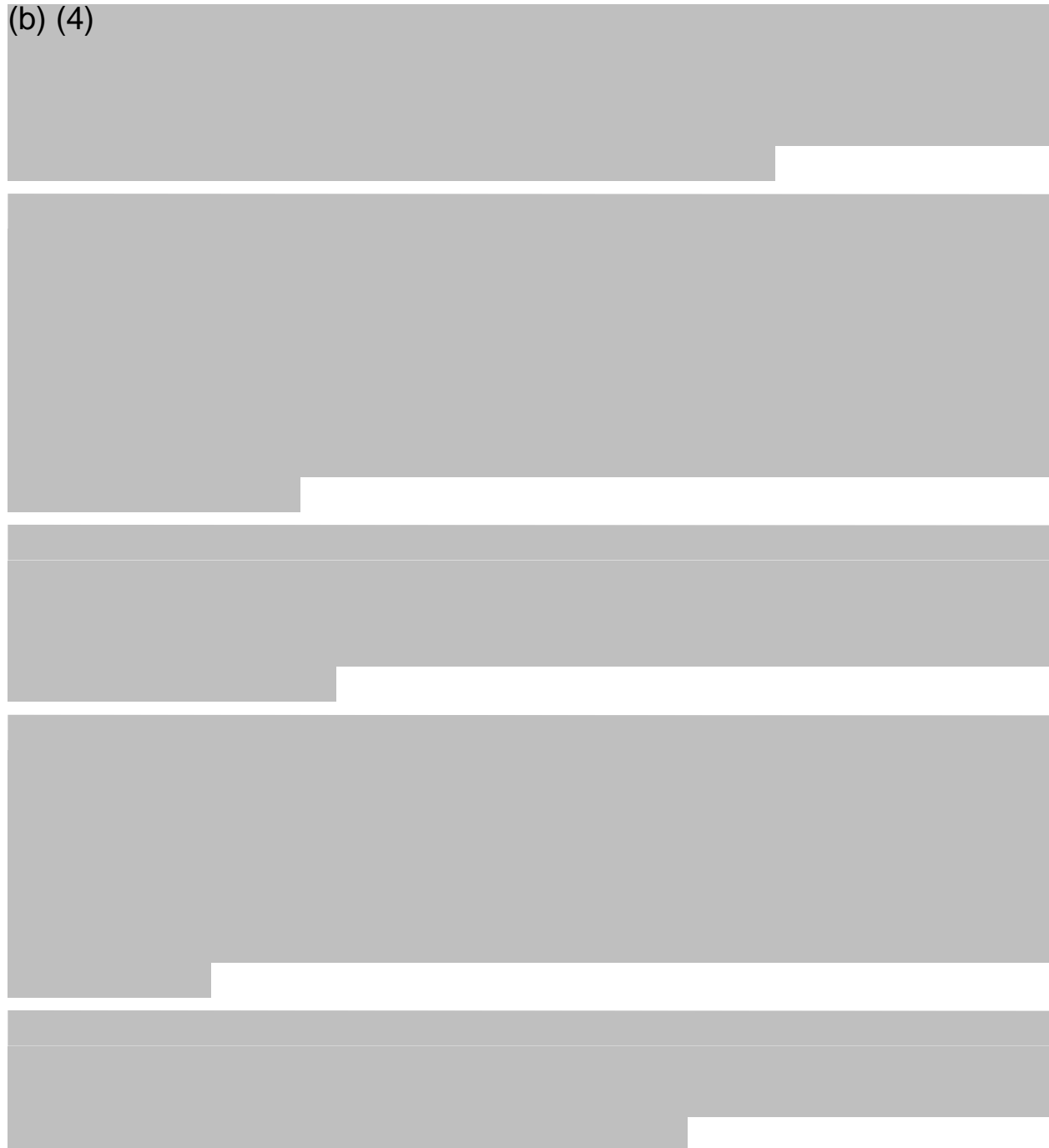
(b) (4)

[REDACTED]

(b) (4)

[REDACTED]

(b) (4)



Conclusions

Validation of the method (b) (6) for IgA (b) (6) 20% IGSC (b) (4) was accomplished through experiments that evaluated linearity, repeatability, intermediate precision, robustness, specificity, accuracy quantitation/detection limits.


Validation acceptance criteria were fulfilled for all parameters tested. The analytical procedure of (b) (4) is considered validated for the

determination of IgA and (b) (4) content in (b) (4), 20% IGSC (b) (4) and is suitable for its intended use.

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


Method

(b) (4)




Validation of Protein Determination by (b) (4) Method

(b) (4)



(b) (4)



Conclusions


Validation of Protein Determination by (b) (4) Method for (b) (4) 20% IGSC was accomplished through experiments that evaluated Repeatability Precision, Intermediate Precision and Specificity.

All the acceptance criteria for all characteristics tested were fulfilled, so Protein Determination by (b) (4) Method is considered validated for the determination of protein in all immune globulin products with (b) (4) polysorbate 80 and is suitable for its intended use.




4. Purity of Protein and Product Identity by (b) (4)

Method


(b) (4)



Validation of (b) (4)



(b) (4)



Conclusions

Validation of test method “Purity of Protein and Product Identity by (b) (4) [redacted]” was accomplished through a series of experiments that evaluated the following characteristics: Linearity/Range, Repeatability Precision, Intermediate Precision, Specificity, Accuracy and LOQ.

Validation acceptance criteria were fulfilled for all characteristics tested. The test method is considered validated and suitable for its intended purpose: quantitative (b) (4) [redacted] IgG related products.