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To: STN: 125683/0

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Subject: Review Memo for Biological License Application for Immune Globulin Subcutaneous (Human), 20%, from Grifols Therapeutics LLC

Summary of Review:

The BLA, STN 125683, was submitted by Grifols Therapeutics LLC to seek approval for its Immune Globulin Subcutaneous (Human), 20% (IGSC 20%), for the treatment of primary humoral immunodeficiency; IGSC 20% is a solution of purified human immunoglobulin (IgG) made from large pools of human plasma.

In the memo, the following analytical methods and their validations, as used for the release testing of IGSC 20% drug product, were reviewed: Glycine Content, pH of (b) (4) protein solution, Polysorbate 80 Content, Protein Concentration, (b) (4) Caprylate Content, and Volumetric Fill Check. Based on the information provided in this submission, all the above-mentioned assays have been validated adequately for their intended uses; approval is recommended for these assays.

Background:

Immune Globulin Subcutaneous, 20% (IGSC 20%), is a solution of purified human immunoglobulin (IgG) made from large pools of human plasma, and aseptically filled into prepared vials of 5 mL, 10 mL, 20 mL, and 50 mL. IGSC 20% is manufactured based on the approved manufacturing process for the Immune Globulin Injection (BLA STN 125046) with a few modifications.

Submitted Information reviewed:

125683

- 1.2 Cover letters
- Cover Letter – Original Application
- 3.2.P. Drug Product [Product-Dosage Form-Manufacturer]

-3.2.P. ig – sc - Grifols

-3.2.P.5. Control of Drug Product

- 3.2.P.5.1. Specification(s)

- GTI_PS-000083 Specifications for Finished Product IGSC 20% (01 Jun 2018)

- 3.2.P.5.2. Analytical Procedures

- Analytical Procedures and Validations (IGSC 20%) (24 May 2018)
- CS-000-BC-036 Glycine (b) (4) (23 Nov 2016)
- CS-000-BC-012 (b) (4) pH in Biological Solutions/Products (16 Jan 2018)
- CS-000-BC-023 Quantitation of Polysorbate 80 by (b) (4) Method (15 Sep 2017)
- CS-000-BC-052 Protein Determination by (b) (4) Method (01 Nov 2017)
- CS-000-BC-028 Determination of Caprylate Using (b) (4) (07 Feb 2017)
- CS-000-BC-007 Volumetric Fill Check (06 Nov 2017)

- 3.2.P.5.3. Validation of Analytical Procedures

- QOAS-2014-102 Validation of Glycine (b) (4) (04 Feb 2015)
- QOAS-2014-098 Method Validation for (b) (4) IGSC 20% using SOP CS-000-BC-012 (b) (4) pH in Biological Solutions/Products (06 Oct 2014)
- BA-RVAL-000005 Validation of Polysorbate 80 by (b) (6) for 20% IGSC (31 Aug 2017)
- QOAS-2015-001 Validation of Protein Determination by (b) (4) Method (10 Feb 2015)
- QOAS-2015-016 Validation of Determination of Caprylate Using (b) (4) (18 Mar 2015)
- BA-RVAL-000004 Validation of Volumetric Fill Check for 20% IGSC (11 Sep 2017)

- 3.2.P.5.4. Batch Analyses

- Batch Analysis (14 Jun 2018)

- 3.2.P.5.6. Justification of Specifications

- BA-RTEC-000082 IGSC 20% Justification of Specifications

125683/0.18 (Amendment) – Recd 01/08/2019 – DATS# 783486

- 1.2 Cover letters

- Cover Letter – Response to Information Request No.13

- 1.12. Other Correspondence

-1.12.11. ANDA Basis for Submission Statement

- Basis for Submission – Response to IR No. 13
- Attachment 1 – Information Request 13 (19 Dec 2018)
- CQAC 18-0003-VR Protein Determination by (b) (4) Method (30 July 2003)
- QOAS-2013-036 Validation Report for the Determination of Caprylate using (b) (4)

Review Narrative:

i) Glycine Content

The release specification for Glycine in IGSC 20% drug product is between (b) (4). The content of Glycine in IGSC 20% drug product is quantified using a (b) (4) method with (b) (4)

Method.

The assay procedures for glycine content determination were described in document #CS-000-BC-036, “Glycine (b) (4)

Sufficient information has been provided in the document, with details on the preparation of calibration standards, and samples, the execution of the method, the validity criteria of the assay result, and the generation of the reportable result.

Validation

This method is validated as a quantitative assay; the following validation characteristics: specificity, system suitability, linearity/range, accuracy, precision, and robustness, were evaluated in the validation report (Doc # QOAS-2014-102: “Validation of Glycine (b) (4)

Specificity of the method was assessed with (b) (4)

(b) (4)

However, the specificity should be assessed with the actual drug product, IGSC 20%, which the method is intended to be used for. An information request (# ii below) was submitted to seek further information.

The system suitability of the method was assessed for the following parameters: (b) (4)

(b) (4)

Hence the system suitability of the method was verified.

Linearity was assessed by (b) (4)

An IR (# i below) was submitted to seek further information.

Precision (repeatability and intermediate precision) of the method was assessed by analyzing (b) (4)

Both repeatability and intermediate precision of the method was validated.

Three accuracy (b) (4)

an information request (# iii below) was submitted to seek further information.

Robustness tests were performed by (b) (4)

the robustness of the method was evaluated.

The range of the assay was established to be between (b) (4) glycine based on the results from precision, accuracy, and linearity of the method. While the precision was reviewed in previous section, the linearity and accuracy data submitted with the original BLA and Amendment 18 were reviewed later.

To evaluate the LOQ, (b) (4)

. Thus, the LOQ of the method was not established. This is acceptable because this is a quantitative assay method for which establishing LOQ of the method is not necessary.

Information request and Review of Responses

The following IR was submitted to the sponsor on 19 December 2018. The response from Grifols was received as Amendment 18 on 8 January 2019.

i) For validation of Glycine (b) (4) (Doc# QOAS-2014-102 and Protocol# QOAS-2014-030), we do not agree that you demonstrated method linearity by (b) (4)

to demonstrate linearity of your method.

Review of Response: The sponsor provided linearity data of glycine in IGSC 20% drug product (b) (4)

Linearity of the method was evaluated successfully.

ii) Specificity was (b) (4)

. Please provide data on the evaluation of specificity using IGSC 20% drug product.

Review of Response:

The sponsor explained that the product IGSC 20% (b) (4) are very similar; IgG purified from human pooled plasma and formulated with 0.2 M glycine at pH about 4.3. The (b) (4) process (b) (4), with only exception that IGSC 20% were further concentrated and contains a small amount PS80 in the formulation. The same glycine assay method is used for all samples, with the exception of the (b) (4), in which samples are (b) (4) glycine (b) (4) IGSC 20% at that (b) (4) would not affect the results of glycine

measurement significantly. In addition, it has been shown from the repeatability study, the average glycine values observed from both IGSC 20% samples (b) (4) found to be equal (b) (4). Hence, the (b) (4) does not affect assessment of glycine significantly. Thus, these results demonstrate method specificity. We are satisfied with their explanation about the specificity evaluation.

iii) You assessed accuracy of the method using (b) (4). This method is intended for the release testing of IGSC 20% drug product, and accuracy needs to be studied with actual drug product. Please provide data on the evaluation of accuracy for IGSC 20% drug product.

Review of Response:

In the response, the sponsor mentioned that they performed a linearity study in response to our IR with (b) (4) of IGSC 20% containing (b) (4) of glycine, which was done in (b) (4). The sponsor (b) (4).

Hence the accuracy for the IGSC 20% matrix was demonstrated.

Based on the information from both original BLA, and Amendment 18, the method has been validated for lot release testing of Glycine content in IGSC 20% drug product.

ii) pH measurement of (b) (4) protein solution

The pH of IGSC 20% was measured using (b) (4) method; the specifications is: (b) (4).

Methods

The assay procedures for pH determination were described in detail in document # CS-000-BC-012 and validated in the document #QOAS-2014-098. Enough information has been provided in the documents, with details on the calibration of the equipment, the operation of the method, and the validity criteria for the assay result. The acceptance criteria for a valid pH test are: (b) (4)

Method Validation

This is a simple method and was verified by examining precision (repeatability and intermediate precision), and accuracy.

Repeatability was evaluated by (b) (4)

(b) (4)

The precision of the method was verified.

Accuracy of the method was verified by (b) (4)

Hence the accuracy of the method was demonstrated.

Based on the information provided, the method has been validated for lot release testing of IGSC 20% drug product.

iii) Polysorbate 80 Content

Polysorbate 80 is formulated into the (b) (4) its release specification for IGSC 20% drug product is 10-40 µg/mL. The polysorbate 80 content in IGSC 20% drug product is determined by a (b) (4) method (CS-000-BC-023: Quantitation of Polysorbate 80 by (b) (4) Method).

Method

The assay procedures for the determination of Polysorbate 80 content in IGSC 20% drug product were described in details in DOC# CS-000-BC-023 (Quantitation of Polysorbate 80 by (b) (4) Method), (b) (4)

Method Validation

This method is validated as a quantitative assay. The following validation characteristics were evaluated in the validation report (BA-RVAL-000005: Validation of Polysorbate 80 by (b) (4) Method for 20% IGSC): precision (repeatability, and intermediate precision), accuracy, linearity/range, specificity, and robustness.

The repeatability of the method was assessed by (b) (4)

(b) (4) The intermediate precision was evaluated by (b) (4)

, and the precision of the method was validated.

The accuracy of the method was evaluated by (b) (4)

and the accuracy of the method was validated.

The data from accuracy were also used to demonstrate the linearity/range of the method. (b) (4)

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

was met, and the specificity of the method was validated.

The robustness of the method was evaluated (b) (4)

IR questions

The following IR questions were submitted on December 19, 2018 to seek further information regarding the Polysorbate 80 method:

For the validation of the Polysorbate 80 content by (b) (4) method (BA-RVAL-000005), we do not agree that you demonstrated method linearity by (b) (4) Polysorbate 80 (b) (4). Such (b) (4) show

(b) (4)

Please provide (b) (4)

to demonstrate linearity of your method.

Review of the response from the sponsor

Grifols Therapeutics provided a response to the IR in Amendment 18 on January 8, 2019.

In response, the sponsor provided the (b) (4)

iv) Protein Concentration

The protein concentration of IGSC 20% drug product is determined by a (b) (4) method (CS-000-BC-052: Protein Determination by (b) (4) Method) and the release specification is 18-22%.

Method

In this procedure, (b) (4)

The provided information is adequate.

Method Validation

In this submission, this analytical method was only partially validated for the protein determination of IGSC 20% drug product (DOC# QOAS-2015-001: Validation of Protein Determination by (b) (4) Method for (b) (4) 20% IGSC). The following validation characteristics were evaluated: precision (including repeatability and intermediate precision), and specificity.

For repeatability, IGSC 20% (b) (4)

(b) (4)

was met, and the precision of the method was validated.

For specificity, (b) (4)

and met the acceptance criterion for specificity, and the specificity of the method was validated.

Further data on the evaluation of the accuracy, linearity, range, and robustness of the method for IGSC 20% drug product were not provided and sought through IR.

IR questions

The following IR questions were submitted on December 19, 2018 to seek further information regarding the Protein Determination by (b) (4) method:

In the validation of the (b) (4) method (DOC# QOAS-2015-001), only precision and specificity were evaluated for IGSC 20%. As you have acknowledged in the submission, (b) (4) for which the method has been fully validated; therefore, the method needs to be fully validated for the testing of IGSC 20%. Please provide data on the evaluation of accuracy, linearity, range, and robustness for IGSC 20% drug product.

Review of the response

On January 8, 2019, Grifols provided responses to the above IR in Amendment 18. In the response, the sponsor indicated that the (b) (4) method has been fully validated for the analysis of (b) (4) and provided the validation report (CQAC 18-0003-VR Protein Determination by (b) (4) Method (30 July 2003)). In the report, the method was evaluated for accuracy, precision, linearity, specificity, and robustness for (b) (4). The sponsor stated that the (b) (4) IGSC 20%: (b) (4) IgGs (b) (4) in 0.2 M glycine solution of pH 4.3, except that IGSC 20% (b) (4), (b) (4) formulated with polysorbate 80 of 25 µg/mL. Because of the similarity, the sponsor considered that the validity of the method for (b) (4) can be applied to IGSC 20%, for the reasons that: i) before being analyzed, (b) (4) drug products are (b) (4) so the difference in the IgG levels in the (b) (4) drug products will not interfere with the results of the method; and ii) the specificity of the method was re-

evaluated in the current BLA for IGSC 20%, (b) (4) with (b) (4) polysorbate 80. The reviewer agrees with the sponsor's assessment and considered that the information provided in Amendment 18 is sufficient, and the method has been validated for the lot release testing of IGSC 20% drug product.

v) (b) (4) Caprylate Content

(b) (4) Caprylate (b) (4)

Determination of Caprylate using (b) (4)

Method

(b) (4)

The description on the analytical method includes information on the preparations of assay reagents, calibration standards, assay control and various test samples, the execution of the method, assay validity criteria, and the generation of the reportable result. For the assay result to be valid, the Caprylate (b) (4)

The provided information is adequate.

Method Validation

The analytical method was only partially validated for IGSC 20% drug product (DOC# QOAS-2015-016: Validation of determination of Caprylate Using (b) (4)

20% IGSC). The following validation characteristics were evaluated: precision (including repeatability and intermediate precision), LOQ/LOD, and specificity.

For repeatability, IGSC 20% (b) (4)

(b) (4)

Further information will be sought through IR.

To evaluate the specificity of the method, (b) (4)

. The specificity of the method was validated.

The LOQ (Limit of Quantitation) of the method was (b) (4)

IR questions

The following IR questions were submitted on December 19, 2018 to seek further information regarding the (b) (4) Caprylate Content method:

- i) For validation of the (b) (4) Caprylate method (DOC# QOAS-2015-016), only precision, specificity, and LOQ were evaluated for IGSC 20%. As you have acknowledged in the submission, the sample matrix of IGSC 20% is different from the sample matrices of (b) (4) for which the method has been fully validated; therefore, the method needs to be fully validated for the testing of IGSC 20%. Please provide data on the evaluation of accuracy, linearity, range, and robustness for IGSC 20% drug product.
- ii) The precision of the method was evaluated by analyzing IGSC 20% (b) (4) caprylate. It is unclear why (b) (4) was chosen for the precision study. Please provide justification. If the measured concentration of caprylate in the actual IGSC 20% drug product is consistently below the LOQ, please provide data evaluating precision of the method at the LOQ level of (b) (4) caprylate.
- iii) After reviewing the batch analysis result, we found that the caprylate concentrations listed for IGSC 20% lots were either (b) (4). Since the LOQ of the method is (b) (4) and the (b) (4), the results below LOQ should be reported as <LOQ and those above LOQ should be reported as actual results. Therefore, it is unclear how test results, such as (b) (4) was obtained. Please clarify.

Review of the response from the sponsor

On January 8, 2019, Grifols provided responses to the above IR questions in Amendment 18.

In response to Question i), Grifols indicated that the analytical method had been validated for (b) (4) by demonstrating its accuracy, linearity, range, and robustness (DOC# QOAS-2013-036), and that (b) (4) IGSC 20% (b) (4) IgG and polysorbate 80 concentrations; thus the partial validation approach in the current submission for IGSC 20% is appropriate. Additionally, the precision, specificity, and LOQ of the method were evaluated for IGSC 20% (b) (4) in this BLA (DOC# QOAS-2015-016: Validation of determination of Caprylate Using (b) (4) 20% IGSC), and the accuracy of the method for IGSC 20% at the (b) (4) IGSC 20% (b) (4) respectively, and met the acceptance criterion for accuracy: (b) (4). With the data provided in both original BLA and Amendment 18, the reviewer agrees with Grifols' approach for the validation of the analytical method for IGSC 20%, and considers the accuracy, linearity, precision, range, and robustness of the method adequately validated.

In response to Question ii), Grifols provided the justification for using (b) (4) Caprylate (b) (4)

The explanation is acceptable.

In response to Question iii), Grifols explained that during the early development, the LOQ of the method was determined to be (b) (4), and IGSC 20% samples were (b) (4) (Validation Report: QOAS-2013-036); after additional development, it was determined that (b) (4) Caprylate (b) (4) IGSC 20% (b) (4)

Since there are no major changes between earlier and current version of the analytical method, (b) (4)

Based on the information from both original BLA, and Amendment 18, the method has been validated for lot release testing of (b) (4) Caprylate in IGSC 20% drug product.

vi) Volumetric Fill Check

The IGSC 20% drug product is packaged in four different fill volumes: 5, 10, 20, and 50 mL. The volumetric fill check of IGSC 20% was determined using a (b) (4) method (DOC# CS-000-BC-007: Volumetric Fill Check).

Method

The volumetric fill check of IGSC 20% drug product is performed based on a (b) (4) method; the details were described in DOC# CS-000-BC-007: Volumetric Fill Check. In brief,

(b) (4)

The description on the analytical method includes information on the preparations of assay reagents, the execution of the method, and the generation of the reportable result. The provided information is adequate.

Method Validation

This (b) (4) method for volumetric fill check is widely accepted. In this submission, it was partially validated for the testing of IGSC 20% drug product (BA-RVAL-000004 Validation of Volumetric Fill Check for 20% IGSC) by only evaluating repeatability, intermediate precision, and accuracy of the method.

To evaluate the repeatability of the method, (b) (4)

, the repeatability of the method was validated.

To evaluate the intermediate precision, (b) (4)

To evaluate the accuracy of the method, (b) (4)

The accuracy of the method was validated.

Because of its simplicity, it is acceptable to only partially validate this method for the release testing of IGSC 20% drug product; with its precision and accuracy evaluated, the method is validated for its intended purpose.