

From: Alicea, Candido
Sent: Wednesday, December 19, 2018 11:34 AM
To: 'Joan.Robertson@grifols.com'
Subject: Information Request #13: STN 125683/0 Grifols Therapeutics LLC Immune Globulin Subcutaneous (Human),

Our Reference: BL 125683/0

Dear Ms. Robertson:

We are reviewing your July 9, 2018, supplement to your biologics license application for Immune Globulin Subcutaneous (Human), 20%. We are requesting that you provide the following information:

1) Polysorbate 80 content by (b) (4) 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.

2) 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, 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.

3) (b) (4) Caprylate Content

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.

4) Glycine (b) (4).

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)

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

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.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

OPTION IF INFORMATION IS BEING REQUESTED:

Please submit your response to this information request as an amendment to this file by January 7, 2019, referencing the date of this request

The action due date for this file is July 9, 2019.

Sincerely,

Candido

Cándido Alicea Ph.D.
CDR, USPHS
Regulatory Project Manager
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 240-402-8310
Fax: 301-595-1303
candido.alicea@fda.hhs.gov

"THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this

document in error, please immediately notify the sender by e-mail or phone."