

From: Do, Yu
Sent: Monday, November 09, 2015 2:25 PM
To: dmyers@malvernconsultinggroup.com
Subject: Information Request (Response Due by Monday, November 23, 2015):
Original BLA, BL 125590/0, Immune Globulin Intravenous (RI-002), ADMA
Biologics, Inc.

Importance: High

Dear Ms. Myers:

We are reviewing your original July 31, 2015 submission to BLA 125590/0 for Immune Globulin Intravenous (Human). We are providing the following comments and request additional information to continue our review:

1. Assay for (b) (4)

a. You propose to report (b) (4) results as a ratio of the average result for the drug product to that of an “internal standard,” which is described as Alert Level Control (ALC) in your SOP document TM-10011. Please provide a complete description of the internal standard identifying difference(s) between the drug product (DP) and the internal standard. Please provide the qualified value of (b) (4) of the internal standard and the details of how the qualified value was determined.

b. If the internal standard (i.e., ALC) is not a representative lot of the drug product, please provide data for the evaluation validation characteristics of specificity, accuracy, repeatability, intermediate precision, linearity, LOQ, range, and robustness using the internal standard because the assay results from the internal standard is as critical as that from DP for the quality control of your product.

c. In your SOP TM-10011, the Working Range of the assay method is defined as (b) (4) and the Lower Limit of Quantitation (LLOQ) as (b) (4). Please explain why LLOQ in your SOP is different from the lower limit of your Working Range. Furthermore, in your validation report (AMVR-20121022-01), you determined the assay range to be (b) (4). Please revise the SOP to make the Working Range consistent with the assay range established in your validation report.

d. Validation report (AMVR-20121022-01) indicates that the validation studies were performed by a contract organization, (b) (4). If routine testing will be performed at a facility other than (b) (4) please provide data from reproducibility and comparability studies to demonstrate that the (b) (4) Assay is transferred to the facility where this assay will be performed.

2. Test for Particulate Matter

a. Regarding the Test for Particulate Matter (STP-0011), you have indicated in 3.2.P.5 Section 3.12 that the “test is performed per compendial method, (b) (4) ... a complete validation is not necessary.” Please submit information that this procedure has been verified for suitability under conditions of use. At a minimum, please submit data for repeatability and intermediate precision obtained for the RI-

002 Injection, Sterile solution.

3. Assay for Protein by (b) (4) Method

- a. You have provided the validation report (VP-FR-0156) but not the validation protocol. We are unable to understand and review some of the validation data without the validation protocol. Please provide the validation protocol.
- b. You have not evaluated accuracy of the assay. Please provide data on accuracy of the method using the drug product.
- c. It is unclear whether the linearity, precision, LOQ, and LOD were evaluated using the drug product or standards. Please clarify. If these validation characteristics were not evaluated using the drug product, please provide data on linearity, precision, LOQ, and LOD of your method using the drug product.
- d. You have evaluated intermediate precision of the assay with inter-analyst difference of (b) (4) analysts, but you have not evaluated inter-day variation. Please provide data on inter-day variation of the assay.
- e. It is unclear how the specificity of the assay was validated. If the study design involves (b) (4) [REDACTED] was not sufficiently addressed. Please provide adequate data to show that there is no effect of the buffer matrix on the assay results to demonstrate specificity of the assay.
- f. Please state the assay range clearly and provide experimental data that verify the range.

The review of this submission is ongoing and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your response as an amendment to this file by November 23, 2015, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is July 30, 2016.

Please acknowledge receipt of this request and contact me at (240) 402-8343 or Yu.Do@fda.hhs.gov if you have any questions.

Sincerely,

Yu Do, M.S.
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