

From: Ovanesov, Mikhail V.
Sent: Wednesday, March 20, 2019 5:25 PM
To: Deng, Lu <Lu.Deng@fda.hhs.gov>
Cc: Virata, Maria Luisa <MariaLuisa.Virata@fda.hhs.gov>; Zhang, Pei <Pei.Zhang@fda.hhs.gov>; Kennedy, Michael <Michael.Kennedy@fda.hhs.gov>; Scott, Dorothy <Dorothy.Scott@fda.hhs.gov>
Subject: RE: ADMA's CR response to STN 125590.0 regarding the (b) (4) assay

Dear Lu,

My review below. Thank you for waiting!

Thank you,
Mikhail

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Review of (b) (4) testing data in ADMA's response to July 29, 2016 Complete Response Letter (CRL).

Reviewed BLA files:

(b) (4) data in the following BLA amendments:

- STN 125590/0.42: under section 1.11.1 (Response to Complete Response Letter of July 29, 2016): CR items 16 and 17
- STN 125590/0.47: (b) (4) analytical procedure and validation under section 3.2.P.5
- STN 125590/0.51 (received 2/22/2019): Response to DBSQC's information request regarding validation of (b) (4) procedure.

Review of response to CRL item 16:

16. You have presented the results of the intermediate precision study as evidence of robustness of the (b) (4) Assay test Method of IGIV Drug Product. This data is insufficient to demonstrate method robustness. Please provide data to evaluate effect of small deliberate changes of critical method parameters, such as reagent concentration, incubation time, etc. in order to demonstrate method robustness.

Summary of ADMA's response: ADMA has been working with (b) (4) to develop a method for measuring (b) (4) in RI-002 using an (b) (4) assay. The (b) (4) assay demonstrates increased sensitivity as compared to the current (b) (4) assay and allows for sample dilution to address matrix effects. (b) (4) conducted a development study including a comprehensive robustness assessment of the (b) (4) assay utilizing the previous ADMA IGIV drug product (Report-2016-1220-01).

Note that ADMA implemented the (b) (4) assay instead of the current (b) (4) assay after the CRL response submission. The (b) (4) method was in use as of February of 2019.

Reviewer's conclusion and comments:

The response is acceptable. The proposed (b) (4) method is suitable for the purpose of accurate quantification of (b) (4) in ADMA's product. The (b) (4) method compares favorably to the methods currently used by the IGIV manufacturers of similar products. The (b) (4) demonstrated improved linearity and robustness and reduced low limit of quantification compared to similar methods reported in the literature and regulatory submissions. The dynamic assay range, (b) (4), covers the typical range of (b) (4) found in marketed IGIV products. The method allows (b) (4) quantification at levels both within and well below the typical allowable levels of (b) (4). Therefore, this method is suitable both for the release of ADMA's product and trending of (b) (4) levels.

ADMA does not specify the nature of assay modifications which were made to improve the assay performance. I have noted the following assay features which are consistent with best practices in (b) (4) testing:

1. (b) (4)

Review of response to CRL item 17:

17. The validation of the (b) (4) Assay for (b) (4) impurity, (b) (4) was deficient and the proposed specifications for this assay were not justified by the impurity characterization studies. Your assay comparability investigation demonstrated a disagreement between the (b) (4) assay and the (b) (4) method, a (b) (4) assay, for the detection of (b) (4). Since both methods were calibrated using the same (b) (4) standard, the discrepancy may indicate the presence of additional impurities detected by only one of these methods or the sensitivity of the (b) (4) Assay to product matrix components (immune globulin protein and excipients). Please investigate the sources of the observed discrepancy between the two methods. The investigation should include, but not be limited to, a side-by-side analysis by both assays of all available Drug Product (DP) lots (to investigate manufacturing consistency) with at least (b) (4) DP batches spike with the purified (b) (4) (to investigate (b) (4) recovery and address effects of matrix), as well as stability studies of representative DP batches. Please consider changes to the analytical conditions of the (b) (4) test that may minimize the discrepancy, including the development of a product-specific standard of (b) (4) using a matrix representative of the DP. The product-specific standard of (b) (4) should be calibrated against the current international standard for (b) (4) and placed on a stability monitoring program.

Summary of ADMA's response: (b) (4) . has developed an (b) (4) assay that has increased sensitivity allowing for sample dilution to address matrix effects. Rather than investigating the sources of discrepancies between the original (b) (4) assay and an (b) (4) method, ADMA intends to replace the existing (b) (4) assay in the BLA with the newly developed (b) (4) assay.

Feasibility experiments have shown that using a minimal (b) (4) dilution of RI-002 in the (b) (4) provided more accurate recovery of spiked (b) (4) when compared to the current (b) (4) assay. When RI-002 was diluted (b) (4) , the recovery was (b) (4) of the spike value in the (b) (4) assay compared to (b) (4) in the current (b) (4) assay. The (b) (4) assay recoveries were (b) (4) for the same RI-002 spiked samples.

ADMA acknowledges that the previous IGIV manufacturing process allowed for more impurities that could interfere with the (b) (4) assay in drug product. The manufacturing consistency and product quality were significantly improved with the optimized ADMA IGIV manufacturing process. Currently the (b) (4) specification in RI-002 is expressed as a ratio between (b) (4) of the DP and the (b) (4) of the Alert Limit Control (ALC) at (b) (4) level. ADMA proposes to change the (b) (4) specification in RI-002 from (b) (4) Ratio to Alert Level Control to (b) (4) based on the (b) (4) results from both (b) (4) method at (b) (4) and in-house (b) (4) method. ADMA plans to continue characterizing the optimized IGIV manufacturing process with the enhanced analytical testing plan in order to gain a full understanding of the process capability. As such ADMA intends to re-establish the (b) (4) specification that reflects the process capability as well as safety after manufacturing a minimum of (b) (4) batches.

Reviewer's conclusion and comments:

The response is acceptable. I agree with ADMA's conclusion that a disagreement between the (b) (4) assay and the (b) (4) method, a (b) (4) assay, was due to matrix interference with the (b) (4) assay. This problem was resolved with the improved (b) (4) assay, because (b) (4) is substantially more sensitive than (b) (4) , allowing (b) (4) of ADMA's product prior to testing. (b) (4) of excipients reduces their interference with the assay. Furthermore, improved robustness of (b) (4) assay allows for accurate (b) (4) testing compared to the original (b) (4) assay and possibly the (b) (4) assay. Importantly, full validation of the (b) (4) assay (submitted in amendment 0.51 dated 2/22/19) included the robustness studies for CRL Item #16 and the stability studies for the assay standard, which are found acceptable.

Review of ADMA's response to IR d:

1. IN AMENDMENT 42, RESPONSE TO COMPLETE RESPONSE LETTER (CR) DATED JULY 29, 2016, SUBMITTED TO STN BL 125590/0 FOR IMMUNE GLOBULIN INTRAVENOUS (HUMAN), 10% LIQUID, YOU INDICATED THAT YOU ARE WORKING WITH (b) (4) TO DEVELOP A METHOD FOR MEASURING (b) (4) IN YOUR IMMUNE GLOBULIN INTRAVENOUS (HUMAN), 10% PRODUCT (RI-002) USING AN (b) (4) ASSAY AND THAT YOU WILL IMPLEMENT THE (b) (4) ASSAY, INSTEAD OF THE CURRENT (b) (4) ASSAY AS SOON AS VALIDATION OF THE METHOD IS COMPLETED WHICH WAS EXPECTED TO BE BY THE END OF DECEMBER 2018. IN AMENDMENT 47 SUBMITTED TO STN BL 125590 ON DECEMBER 21, 2018, RESPONSE TO FDA REQUEST FOR INFORMATION – TESTING AND ANALYTICAL ASSAYS – 11 DECEMBER 2018, YOU PROVIDED A LIST OF CHANGES YOU MADE TO THE ANALYTICAL METHODS USED FOR RI-002 DRUG SUBSTANCE AND FINAL CONTAINER DRUG PRODUCT SINCE THE ISSUANCE OF THE CR LETTER DATED JULY 29, 2016. HOWEVER, YOU DID NOT INCLUDE (b) (4) ASSAY IN YOUR LIST.

Summary of ADMA's response:

The (b) (4) assay validation for measuring (b) (4) is complete. The method validation was ongoing at the time of STN BL 125590/0 sequence 0047 amendment dated December 21, 2018. As a result, the (b) (4) assay was not included in the list of analytical methods in the Response to FDA Request for Information – Testing and Analytical Assays – 11 December 2018. The (b) (4) assay demonstrates increased sensitivity as compared to the current (b) (4) assay and allows for sample dilution to address matrix effects. Sections 3.2.P.5.2.20 and 3.2.P.5.3.20 have been updated to reflect the validated assay. The SOP number for (b) (4) testing has changed, and all applicable sections will be updated to reflect this change during the annual report. The current release specifications remain acceptable for the new assay. The new (b) (4) assay validation demonstrates better accuracy, enhanced sensitivity and a more complete robustness. The (b) (4) Validation and the (b) (4) SOP is included for review.

Reviewer's conclusion and comments:

The response is acceptable. I agree with ADMA's conclusion that (b) (4) assay validation demonstrates better accuracy, enhanced sensitivity and a more complete robustness, and that the current release specifications remain applicable for the new assay.

Regarding the validation of (b) (4) assay, I agree with the DBSQC reviewer who found deficiencies with the design of the (b) (4) method validation studies regarding the assay linearity and range (ADMA used assay results, expressed in (b) (4) units rather than the assay readouts expressed in units of (b) (4)). The deficiencies identified by DBSQC are important to assure consistency in implementation of ICH and FDA guidance recommendations regarding analytical assay validation. DBSQC often finds similar deficiencies in original BLA assigned to our product office, supporting the importance of DBSQC expertise. In this case, the analytical assay validation deficiencies do not mean that the method is not working. Importantly, the results of (b) (4) method validation studies are acceptable since the existing evidence suggests good performance of the method. DBSQC's additional experiments are expected to confirm this favorable assessment, but it may take some weeks to conduct these experiments. Therefore, I recommend that these deficiencies should be addressed with additional method validation experiments, but they should not delay the approval of the BLA.

2. IF YOU INTEND TO USE THE (b) (4) ASSAY FOR THE DETERMINATION OF (b) (4), INSTEAD OF THE (b) (4) ASSAY METHOD, PLEASE PROVIDE DATA TO EVALUATE EFFECT OF SMALL DELIBERATE CHANGES OF CRITICAL METHOD PARAMETERS, SUCH AS REAGENT CONCENTRATION AND INCUBATION TIME, IN ORDER TO DEMONSTRATE METHOD ROBUSTNESS, AS REQUESTED IN THE COMPLETE RESPONSE LETTER.

Summary of ADMA's response:

ADMA has implemented the validated (b) (4) assay for lot release of RI-002 and does not intend to use (b) (4) assay for the determination of (b) (4) for commercial production.

Reviewer's conclusion and comments:

The response is acceptable.

From: Deng, Lu

Sent: Thursday, January 17, 2019 2:52 PM

To: Ovanesov, Mikhail V. <mikhail.ovanesov@fda.hhs.gov>
Cc: Virata, Maria Luisa <MariaLuisa.Virata@fda.hhs.gov>; Zhang, Pei <Pei.Zhang@fda.hhs.gov>;
Kennedy, Michael <Michael.Kennedy@fda.hhs.gov>; Scott, Dorothy <Dorothy.Scott@fda.hhs.gov>
Subject: ADMA's CR response to STN 125590.0 regarding the (b) (4) assay

Hi Mikhail,

Thanks for agreeing to be the consult. The following Amendments contain the information on (b) (4) assay from ADMA.

STN 125590/42: under section 1.11.1 (Response to Complete Response Letter of July 29, 2016) **CR items 16 and 17**

STN 125590/47: (b) (4) analytical procedure and validation under section 3.2.P.5

Thank you very much!

Lu