



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: BLA STN 125590/0 File

From: Maria L. Virata-Theimer, Ph.D., Chemist, OTAT/DPPT/PDB
Lu Deng, Ph.D., Biologist, OTAT/DPPT/PDB

Through: Michael C. Kennedy, Ph.D., Team Leader, OTAT/DPPT/PDB

CC: Yu Do, M.S., RPM, OTAT/DRPM

Applicant: ADMA Biologics Inc., Ramsey, NJ

Product: Immune Globulin Intravenous (Human), 10% Liquid
Proposed Trade name: ASCENIV

Subject: CMC Review: Original BLA Resubmission – Drug Substance and Drug Product Specifications, Analytical Procedures and their Validation Studies assigned to the Product Office – Responses to Complete Response Letter dated 29-JUL-2016

Recommendation

Approval – with regards to the (b) (4) Drug Product Specifications, and the following Analytical Procedures and their Validation Studies that were reviewed by the Product Office:
Appearance, pH, (b) (4) Residual Triton X-100, Residual Tri-n-Butyl Phosphate, Residual Ethanol, Total IgA, (b) (4) Potency-Polio, Potency-Measles, Potency-Anti-Hepatitis B surface antigen, Chloride, (b) (4) Purity, Glycine, Identity, (b) (4)

BLA Resubmission Executive Summary

This Discipline Review memorandum covers the review of Complete Response (CR) Letter items associated with the CMC sections we had reviewed previously in the first review cycle for the original Biologics License Application (BLA) submission from ADMA Biologics Inc., for Immune Globulin Intravenous (Human)(IGIV), 10% Liquid, ASCENIV (RI-002). The CMC sections we reviewed were the Drug Substance and Drug Product Specifications, and several Analytical Procedures and their Validation Studies assigned to the Product Office. Mikhail Ovanesov, Ph.D. of OTAT/DPPT/HB was consulted regarding the (b) (4) assay. In general, most of the information provided by ADMA for these sections in their responses to the CR Letter and our information requests were acceptable and adequate. The issues concerning the implication of an (b) (4) disease indication claim were brought up again during this review cycle due to ADMA's new proposal to use the (b) (4) test as an identity test, which FDA disagreed with. These (b) (4) issues were only resolved after the sponsor finally agreed to FDA's request to remove any mention of (b) (4) from their Drug Product Specifications, Certificate of Analysis, package insert, lot release protocol template, and promotional materials (see the Meeting Minutes of the 6-MAR-2019 Type C Meeting teleconference). FDA allowed ADMA to continue testing and monitoring the (b) (4) for internal purposes only, through their manufacturing batch records. In addition, FDA decided to accept ADMA's original proposal to use the (b) (4) method as the identity test for identifying human IgG, because of current hospital and pharmacy practices in placing IGIV orders.

Resubmission Review Summary

FDA CBER received on 1-OCT-2018 this BLA Resubmission package (Amendment 42, dated 28-SEP-2018) for the original BLA STN 125590/0 from ADMA Biologics Inc., for Immune Globulin Intravenous (Human)(IGIV), 10% Liquid, ASCENIV (also referred to internally by the sponsor as RI-002). RI-002's proposed indication is for the treatment of patients with primary humoral immunodeficiency. Manufacture, in-process and most of the lot release testing of RI-002 are performed at the Biotest Pharmaceutical Corporation (BPC) facility in Boca Raton, FL. ADMA purchased BPC on 6-JUN-2017, therefore, ADMA now owns the Boca Raton, FL facility. Aseptic filling of 50 mL final container vials is performed at (b) (4). However, as of this BLA Resubmission, ADMA has added a second contract filling site, (b) (4) for filling the 50 mL vials.

Product Reviewer's Comment: *The sponsor had indicated in various sections of the BLA that aseptic filling at the (b) (4) facility may be done using 50 mL (b) (4) vials, however, to date, only 50 mL conformance lots filled by (b) (4) have been submitted for review. For this BLA Resubmission, the sponsor submitted 3 new 50 mL conformance lots filled by (b) (4)*

A. Responses to the 29-JUL-2016 Complete Response Letter Items nos. 13 and 17 (Amendment 42, received 28-SEP-2018)

1. FDA CR item #13

For the identity test of RI-002, you proposed to develop a method SOP which will be based on the Identity test method Biotest Pharmaceuticals Corporation (BPC) is using for Nabi-HB (SOP LAB3014).

- A. Please provide your method SOP for the Identity testing of labeled RI-002 final container product lots, which should include details on which positive and negative controls will be used, how the dilutions of test samples and controls will be prepared, what the positive result cut-off will be (and how it was determined), and a section on valid tests and retesting.**
- B. Please validate your proposed method according to ICH/FDA guidelines on analytical method validation (e.g.: testing a sufficient number of labeled product lots of RI-002, Nabi-HB, and other BPC products, if possible) and provide the method validation results.**

ADMA did not provide what was requested in this CR item. Instead of following through with their previous proposal of using the Anti-HBs test method for identity testing of RI-002 (see Amendment 34, received 4-MAY-2016), ADMA newly proposed to use the (b) (4) potency assay as the identity test to differentiate RI-002 from other ADMA immune globulin products produced in the Boca Raton, FL facility. They stated that an SOP for identity testing will be developed after completion of the validation for RI-002's identity test method. In addition, they said that RI-002 final vial drug product can also be differentiated from the other immune globulin products by a visual inspection of seal color. RI-002 is the only ADMA-produced immune globulin product for which container closure set-up requires a blue colored flip-off seal as part of the vial container closure specifications.

Product Reviewer's comments: *(1) We had already communicated to the sponsor in the previous review cycle (July 2015 – July 2016) our past concerns about including (b) (4) verbiage which could imply an (b) (4) disease treatment claim without the supporting clinical data, therefore, we disagree with ADMA's new proposal to use the (b) (4) test for identity testing of RI-002. Information Requests (IR) were sent to the sponsor on 30-OCT-2018 and 2-NOV-2018 to reiterate our previous request that they remove any mention of (b) (4) from the package insert, list of specifications, Certificate of Analysis and lot release protocol (LRP) template. In their responses to this IR (see Amendments 44 and 45, received 5-NOV-2018 and 30-NOV-2018, respectively), instead of agreeing to our request, ADMA asked to set up a meeting with FDA to discuss possible legal issues (e.g., adulteration, misbranding, disclosure of using (b) (4) in the*

package insert, etc.). The formal meeting request from ADMA was received on 12-FEB-2019 (see Amendment 48) and a Type C Meeting teleconference with the sponsor took place on 6-MAR-2019.

During the Type C Meeting held on 6-MAR-2019, the sponsor finally agreed to FDA's request to remove any mention of (b) (4) from their Drug Product Specifications, Certificate of Analysis, package insert, lot release protocol template, and promotional materials (see the Meeting Minutes Summary of the 6-MAR-2019 Type C Meeting teleconference). FDA allowed ADMA to continue testing and monitoring the (b) (4) for internal purposes only, through their manufacturing batch records. In addition, FDA decided to accept ADMA's original proposal to use the (b) (4) method as the identity test for identifying human IgG, because of current hospital and pharmacy practices in placing IGIV orders. Based on what was agreed upon during the Type C Meeting, ADMA sent their revised responses to the 2-NOV-2018 IR in Amendment 54 (received 12-MAR-2019) with the revised Drug Product Specifications, lot release protocol template and package insert that do not contain any mention of (b) (4). The sponsor also submitted a new Batch Production Record form for tracking (b) (4) for internal purposes only (see form F-SAF3061-a (b) (4) Potency Tracking for Asceniv (RI-002) Batch Production). The form shows that (b) (4) will be reported for the (b) (4) final Drug Product (acceptance criteria: (b) (4) of Reference Standard). These responses are acceptable.

(2) We consulted Dr. Judy Beeler of OVRP/DVP/LPRV regarding the (b) (4) issues. She did a comprehensive review of the (b) (4) test documents provided by ADMA to date, especially since the sponsor had indicated that the (b) (4) testing had been transferred from (b) (4) to (b) (4). The latest version of the (b) (4) method SOP (PDR ATM AHX-0001, version 2.0, dated 4-SEP-2018) and the method transfer and assay control sample qualification study report (TTP-AHX-M0004, dated 23-APR-2018) were submitted in Amendment 42 (received 28-SEP-2018).

Consult Reviewer's Comments (see Dr. Beeler's review memo dated 5-MAR-2019 for more details and comments): (1) "The (b) (4) assay performed by (b) (4) appears to be similar to that developed by (b) (4), for development and testing of (b) (4) licensed previously by (b) (4). However, it is unclear from the documents reviewed if (b) (4) has sufficient checks in place to assure that the assay is valid in all respects."

(2) "It is this reviewer's opinion that the sponsor has made a good attempt to validate the (b) (4) assay, however, there are a few questions about the assay that still need to be addressed particularly if the sponsor intends to use this test for lot release. If the sponsor intends to use this test for lot release, a biostatistician should review the validation data as well."

2. FDA CR item #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.

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 2019.

Product Reviewer's Comment: We consulted Mikhail Ovanesov, Ph.D., of OTAT/DPPT/HB for reviewing the CR responses related to the (b) (4) assay. He reviewed the (b) (4) documents and 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 22-FEB-2019): Response to DBSQC's information request regarding validation of (b) (4) procedure.

Leslyn Aaron of OCBQ/DBSQC/LACBRP also reviewed the CR responses related to the (b) (4) assay and additional responses to IRs sent on 22-FEB-2019 and 4-MAR-2019 (see her review memo dated 21-MAR-2019).

Consult Reviewer's Comments (see Dr. Ovanesov's email dated 20-MAR-2019): "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)

(b) (4)

3. FDA CR item #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.

(b) (4) has developed an (b) (4) assay (b) (4) 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. Preliminary 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 as shown in Table 1. 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 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 shown in Table 2. 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.

Consult Reviewer’s Comments (see Dr. Ovanesov’s email dated 20-MAR-2019): “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.”

B. Responses to 11-DEC-2018 Information Request (Amendment 47, received 26-DEC-2018)

- 1. Please provide a complete list of changes you made in all the analytical assays used for RI-002 (b) (4) drug product final container since the issuance of the CR letter dated July 29, 2016.**

ADMA provided a list of changes in the analytical methods since the issuance of the CR letter dated 29-JUL-2016 (Table 1 below).

Table 1: List of changes in the analytical methods since the issuance of the CR Letter dated 29-JUL-2016

| Product Attribute | Method | Description of Changes |
|-----------------------------|-------------------|---|
| Protein | (b) (4) | (b) (4) |
| Total IgA | (b) (4) | (b) (4) |
| Appearance | Visual Inspection | Incorporated the use of (b) (4) compendial reference standards for color and clarity. |
| Identity (Human) (b) (4) | (b) (4) | (b) (4) |
| Potency: Diphtheria | (b) (4) | Method SOP number changed. No procedure changes |
| Potency: Measles | Neutralization | Qualified CBER Reference Standard Lot 177 against CBER Reference Standard Lot 176. No changes were made to the procedure. |

| | | |
|----------------|----------------|---|
| Potency: Polio | Neutralization | Qualified CBER Reference Standard Lot 177 against CBER Reference Standard Lot 176. No changes were made to the procedure. |
|----------------|----------------|---|

Reviewer's Comments: (1) The change in (b) (4) to (b) (4) was submitted by BPC previously for Bivigam (b) (4). It was reviewed and recommended for approval by the Product Office, however, (b) (4) on BPC at the time, therefore, a CR Letter was issued to BPC instead on (b) (4).

(2) See Responses to IR Questions no. 3 and 4 below regarding the qualification of CBER Reference Standard Lot 177 vs. CBER Reference Standard Lot 176 for use in the Potency-Measles and Potency-Polio tests.

2. Two different SOP numbers are listed for "Potency: Diphtheria". Please clarify.

Please also indicate which SOP was used to test the conformance lots submitted in STN 125590/0.42 and which SOP will be used for future RI-002 lots. Please provide SOP-eQC-0251.

- (b) (4), QM/1143" under eCTD section 2.3.R Regional Information-Methods Validation Package
- (b) (4) SOP-eQC-0251" under eCTD section 3.2.P.5.1 Control of Drug Product: Specifications

The current SOP number for "Potency: Diphtheria" is SOP-eQC-0251. The conformance lots submitted in STN 125590/0.42 were tested per this SOP.

The original SOP for Diphtheria method used for release of RI-002 drug product was QM/1143 from (b) (4). The (b) (4) site responsible for Diphtheria testing became part of (b) (4) and for administrative purposes, the SOP number changed from QM/1143 to SOP-eQC-0251 in October 2017. Only the SOP number changed; the methodology and procedure remained identical between the two SOPs.

Additionally, as indicated in ADMA's response dated 28-SEP-2018 to the Complete Response Letter, ADMA has identified a potential alternate CRO lab for the concentration of diphtheria antitoxin antibodies in the RI-002 drug product using an antibody (b) (4) method based on (b) (4) for diphtheria antitoxin. (b) (4) located in (b) (4), completed a feasibility study which confirmed the compendial diphtheria assay currently performed at their facility is suitable for RI-002. A formal compendial assay verification protocol for RI-002 has been approved and testing has been initiated. Per regulatory requirements, ADMA will communicate with FDA prior to making a change in the diphtheria testing site.

Product Reviewer's Comments: (1) The sponsor's response to this IR is acceptable.

(2) Simleen Kaur of OCBQ/DBSQC/LMIVTS reviewed the Diphtheria (b) (4) test for DP (SOP QM/1143/03: Diphtheria Antitoxin Assay) from (b) (4) (see her review memo dated 15-APR-2016). As of the writing of this memo, the feasibility study report for the alternate testing site, (b) (4) has not yet been submitted to the BLA file.

3. To support your use of CBER Lot 177 for anti-measles testing, please provide the following:

- a. Your qualification report VP-FR-4169
- b. A direct comparison of actual anti-measles titers of CBER Reference Lot 176 vs. CBER Lot 177 tested side-by-side (i.e., both reference lots tested in the same run) from at least 30 valid independent test runs. Please submit the raw data and resulting arithmetic mean titers, geometric mean titers, standard deviations, geometric mean titer (natural log transformed), geometric coefficient of variation, ratio of geometric means (Lot 177 to Lot 176) and percent difference of geometric means (Lot 177 to Lot 176).

The sponsor provided the requested qualification report, VP-FR-4169 “Final Report for Qualification of the CBER Candidate Reference Standard Lot 177 for the (b) (4) Assay for Detection of Measles Antibodies Performed According to SOP V6807/04-13 by (b) (4), which contains Quality Control data obtained from valid QC testing performed by (b) (4) from 18-JAN-2013 to 30-OCT-2015 for a total of (b) (4) separate assays.

Due to the limited availability of CBER Reference Lot 176 from FDA, the sponsor did not conduct a side-by-side testing of CBER Lots 176 and 177 in the same runs. Instead, a statistically sound data set (b) (4) was collected to compare the two CBER standard lots using the (b) (4) for anti-Measles (b) (4) with an assigned measles antibody titer of (b) (4), as a (b) (4) standard. Half of the runs (b) (4) assays) were performed by side-by-side testing of CBER Reference Lot 176 and the (b) (4) together in the same runs. The other half (b) (4) assays) were performed by side-by-side testing of CBER Lot 177 and the (b) (4) together in the same runs. The sponsor provided the raw data of the anti-measles titers of CBER Reference Lot 176 and CBER Lot 177 as well as the requested statistical analysis results in Tables 3a and 3b (see Section 1.11.1 - Response to Information Request of December 11, 2018, Amendment 47).

Product Reviewer’s Comments: The sponsor used the qualification data of each of the two CBER Lots to the (b) (4) to bridge the comparisons between CBER Lots 176 and 177, which is an acceptable approach. Table 3a listed the raw data results (mean endpoint titers in IU/mL and in IU/mL Natural Log) of CBER Lot 177 from Test nos. (b) (4) and of CBER Reference Standard Lot 176 from Test nos. (b) (4). The amount of data they provided from (b) (4) was more than adequate for the statistical analysis. See Table 2 below for the calculated statistical parameters (taken from Table 3b in Section 1.11.1, Amendment 47), which appear to be acceptable.

Table 2: Calculated Statistical Parameters – (b) (4) Assay for Detection of Measles Antibodies Performed by (b) (4) per SOP V-6807/04-13

| Calculated Statistical Parameter | CBER RS Lot 176 (16.5% IgG) | CBER RS Lot 177 (10% IgG) | CBER RS Lot 177 (Normalized for IgG Concentration) |
|---|--------------------------------|------------------------------|--|
| Arithmetic Mean End-Point Titer | (b) | (4) | (4) |
| Geometric Mean End-Point Titer (Excel) ¹ | | | |
| Standard Deviation | | | |
| Geometric Mean End-Point Titer (Natural Log Transformed) ² | | | |
| Geometric Standard Deviation ³ | | | |
| Geometric Coefficient of Variation ⁴ | | | |
| Ratio of Geometric Means [*] | | | |
| Percent Difference of Geometric Means ^{5*} | | | |

1. Geometric Mean: = GEOMEAN(a₁:a_n)
2. Geometric Mean (Natural Log Transformed): = EXP(AVERAGE(LN(a₁:a_n)))
3. Geometric Standard Deviation: = EXP(STDEV(LN(a₁:a_n)))
4. Geometric Coefficient of Variation: = Geometric Standard Deviation^(1/Geometric Mean)
5. Percent Difference of Geometric Means: = (ABS(GeoMean₁₇₆ - GeoMean₁₇₇)/AVERAGE(GeoMean₁₇₆, GeoMean₁₇₇))*100

*Normalized value of GeoMean₁₇₇ is used for these calculations

Based on these statistical calculations, the sponsor proposed an alternate Drug Product specification for the Potency – Measles test, when using CBER Lot 177: (b) (4) CBER Ref Std Lot 177. The (b) (4) CBER Lot 177 specification was calculated from dividing the (b) (4) CBER Ref Std 176 specification by the Ratio of Geometric Means (b) (4). The proposed alternate specification is acceptable.

4. To support your use of CBER Lot 177 for anti-polio testing, please provide the following:
 - a. Your qualification report VP-FR-4139
 - b. A direct comparison of actual anti-polio titers of CBER Reference Lot 176 vs. CBER Lot 177 tested side-by-side (i.e., both reference lots tested in the same run) from at least 30 valid independent test runs. Please submit the raw data and resulting arithmetic mean titers, geometric mean titers, standard deviations, geometric mean titer (natural log transformed), geometric coefficient of variation, ratio of geometric means (Lot 177 to Lot 176) and percent difference of geometric means (Lot 177 to Lot 176).

The sponsor provided the requested qualification report, VP-FR-4139 “Final Report for Qualification of the CBER Candidate Reference Standard Lot 177 for the (b) (4) Assay for Detection of Polio Antibodies Performed According to SOP V7205/01-16 by (b) (4)”, which contains historical Quality Control data obtained from valid QC testing performed by (b) (4) from 21-FEB-2014 to 16-AUG-2016 for a total of (b) (4) separate assays.

The sponsor provided the side-by-side retrospective raw data of the anti-polio titers of CBER Reference Lot 176 and CBER Lot 177 as well as the calculated statistical parameters in Tables 4a and 4b (see Section 1.11.1 - Response to Information Request of December 11, 2018, Amendment 47).

Product Reviewer’s Comments: The sponsor provided the side-by-side testing data as requested. Table 4a listed the raw data results (mean endpoint titers in IU/mL and in IU/mL Natural Log) of CBER Lot 177 vs. CBER Reference Standard Lot 176. The amount of data they provided from (b) (4) was adequate for the statistical analysis. See Table 3 below for the calculated statistical parameters (taken from Table 4b in Section 1.11.1, Amendment 47), which appear to be acceptable.

Table 3: Calculated Statistical Parameters – Polio Virus Neutralization Assay Performed by (b) (4) per SOP V-5355/04-09

| Calculated Statistical Parameter | CBER RS Lot 176 (16.5% IgG) | CBER RS Lot 177 (10% IgG) | CBER RS Lot 177 (Normalized for IgG Concentration) |
|---|--------------------------------|------------------------------|--|
| Arithmetic Mean End-Point Titer | (b) | (4) | (4) |
| Geometric Mean End-Point Titer (Excel) ¹ | | | |
| Standard Deviation | | | |
| Geometric Mean End-Point Titer (Natural Log Transformed) ² | | | |
| Geometric Standard Deviation ³ | | | |
| Geometric Coefficient of Variation ⁴ | | | |
| Ratio of Geometric Means | | | |
| Percent Difference of Geometric Means ⁵ | | | |

1. Geometric Mean: = ROUND(GEOMEAN(a₁:a_n),0)
2. Geometric Mean (Natural Log Transformed): = ROUND(EXP(AVERAGE(LN(a₁:a_n))),0)
3. Geometric Standard Deviation: = EXP(STDEV(LN(a₁:a_n)))
4. Geometric Coefficient of Variation: = Geometric Standard Deviation^(1/Geometric Mean)
5. Percent Difference of Geometric Means: = (ABS(GeoMean₁₇₆:GeoMean₁₇₇)/AVERAGE(GeoMean₁₇₆:GeoMean₁₇₇))*100

*Normalized value of GeoMean₁₇₇ is used for these calculations

Based on these statistical calculations, the sponsor proposed an alternate Drug Product specification for the Potency – Polio test (Type 1), when using CBER Lot 177: (b) (4) CBER Ref Std Lot 177. The (b) (4) CBER Lot 177 specification was calculated from dividing the (b) (4) CBER Ref Std 176 specification by the Ratio of Geometric Means (b) (4). The proposed alternate specification is acceptable.

C. Responses to 8-FEB-2019 Information Request (Amendment 49, received 15-FEB-2019)

1. We noted several discrepancies in your wording of the Drug Product specification for Appearance after comparing the following eCTD section files:
 - eCTD section 2.3.R Method Validation Package: “Clear to slightly opalescent. Colorless to pale yellow. Free of turbidity”
 - eCTD section 2.3.P Control of Drug Product: “Clear or slightly opalescent. Colorless or pale yellow. Free of turbidity. Essentially Free of visible particles.”
 - eCTD section 3.2.P.5.1 Specifications: “Clear or slightly opalescent. Colorless or pale yellow. Free of turbidity. Essentially free of visible particles.”
 - eCTD section 3.2.P.5.4 Batch Analyses: “Slightly opalescent; clear. Colorless to pale yellow. Free of turbidity. Free of visible particles.”
 - eCTD section 3.2.P.8.1 Stability Summary and Conclusion: “Clear to opalescent. Colorless to pale yellow. Free of turbidity. Free of visible particles.”
 - eCTD section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment: “Clear to Slightly Opalescent. Colorless to Pale Yellow. Free of Turbidity. Free of Visible Particles.”

Please revise the wording of the Appearance specification in the abovementioned eCTD section files so that they all consistently state: “Clear to slightly opalescent. Colorless to pale yellow. Free of turbidity. Free of visible particles.”

The sponsor concurred that the wording should be aligned and requested consideration on using the following verbiage for the Appearance specification. “Clear to slightly opalescent. Colorless to pale yellow. Free of turbidity. Essentially free of particles.”

ADMA requested using “Essentially free of particles” in order to align with the wording and intent of (b) (4) [REDACTED] Any drug product vial determined to contain a visible particle during final release or stability Appearance testing will continue to be treated as a deviation, which will be thoroughly investigated for root cause and the product quality impact will be assessed. Appropriate BPDR notifications will be sent to the Agency.

Product Reviewer’s Comment: We disagree with sponsor’s request to use “Essentially free of particles” in the Appearance specification. We informed the sponsor on 20-FEB-2019 that we disagreed with their proposal and repeated our request to state “Free of visible particles” in the Appearance specification. The sponsor responded to our request on 26-FEB-2019 (Amendment 52, received 26-FEB-2019) by updating

the Appearance specification with “Clear to slightly opalescent. Colorless to pale yellow. Free of turbidity. Free of visible particles” in the abovementioned eCTD sections.

- You have submitted SOP QC3230, which is an integral part of the Appearance assay, however, SOP QC3230 is not referenced in the Visual Evaluation SOP QC2130, Rev. 10. Please update SOP QC2130, such that SOP QC3230 is included in Section 5 References. Please also indicate which version of QC2130 was used for testing RI-002 conformance lots.**

ADMA acknowledges that QC2130, Rev. 10 did not make reference to the critical procedure for Opalescence QC3230. This was due to a linking error in the updated submission that linked back to the original BLA submission for RI-002 from 2016 as this SOP has been revised since that time to include reference to QC3230. As part of the Biotest site 483 responses to the 2016 FDA inspection of the Boca Raton facility, Opalescence standards were added to align with the (b) (4) and reference to QC3230 was added as a reference to QC2130, Rev. 12 effective 10-MAY-2016. The reference to QC3230 has remained in QC2130 since 10-MAY-2016 through all revisions to the SOP for other matters. QC2130 has also been updated to include Yellow reference color standards, as outlined in Table 1 (see Table 1: *QC2130 Revision Number and Short Description of Change* in Section 1.11.1, Amendment 49, received 15-FEB-2019)

QC2130 Rev. 15 is the latest version used for RI-002 testing.

Product Reviewer’s Comment: The sponsor’s response to this IR is acceptable.

D. Responses to the 12-FEB-2019 Information Request (Amendment 51, received 22-FEB-2019)

- 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 (b) (4) 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.

To this date, we have not received the test procedure and method validation report for the (b) (4) method. Please provide the detailed test method for the (b) (4) and the method validation results for review, if you intend to use this method for the determination of (b) (4) in your Immune Globulin Intravenous (Human), 10% product (RI-002) for lot release.

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.

Consult Reviewer's Comments (see Dr. Ovanesov's email dated 20-MAR-2019): "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.**

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.

Consult Reviewer's Comment (see Dr. Ovanesov's email dated 20-MAR-2019): "The response is acceptable".

E. Response to 20-FEB-2019 Information Request (Amendment 52, received 26-FEB-2019)

1. **Regarding your response to Question 1 of FDA's Information Request dated February 8, 2019, we disagree with your proposed verbiage "Essentially free of visible particles" in the Drug Product Appearance specification. Please revise the wording of the Appearance specification to "Clear to slightly opalescent. Colorless to pale yellow. Free of turbidity. Free of visible particles."**

The sponsor agreed to our request to update the eCTD sections with revised wording we provided. The following sections were updated: 2.3.R. Method Validation Package, 2.3.P Control of Drug Product, 3.2.P.5.1 Specifications, and 3.2.P.5.4 Batch Analysis. Section 3.2.P.8.1 Stability Summary and Conclusions lists the previous specification for historical clinical trial data, however, the new specification for the optimized process data is also listed and is aligned with the specification we provided, and the section is compliant with our request. Section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment states the currently proposed language and is compliant with the request.

Product Reviewer's Comment: The sponsor's response to this IR is acceptable.

F. Responses to 2-NOV-2018 Information Request (Amendment 54, received 12-MAR-2019)

1. **Response to CR Item # 13 letters A and B, re: Identity test of RI-002**

We disagree with your new proposal to use the (b) (4) test for Identity testing of RI-002. To reiterate our past concerns about the inclusion of (b) (4) without substantial clinical efficacy data, please remove any reference to (b) (4) and (b) (4) from your product Certificate of Analysis, product release specifications, lot release protocol, labeling, and promotional materials.

The (b) (4) test was removed from the Product Release Specifications (section 3.2.P.5.1), lot release protocol and labeling for RI-002. ADMA stated that they do not currently have any promotional materials which require update. Product Certificates of Analysis for the conformance batches will be updated to remove any reference to (b) (4) prior to commercial lot release.

Additionally, ADMA has generated a Batch Production Form to track (b) (4) potency for RI-002 as agreed in the Type C Meeting of 06-MAR-2019. ADMA will be using the form (b) (4) Potency Tracking for Asceniv (RI-002) Batch Production” to track (b) (4) Drug Product during RI-002 manufacturing. This form will be attached to their batch record MP60002640 (b) (4) and MP60002650 (RI-002 (b) (4) and (b) (4) Batch Record PRD.BAT.010.00 (Filtration and Fill of RI-002).

Product Reviewer’s Comments: (1) The sponsor’s responses to this IR are acceptable.
(2) The information about the (b) (4) of RI-002 can be used in ADMA’s future clinical studies.

2. **Response to CR Item # 18 letter B, re: removal of (b) (4) from the LRP template**
You retained the (b) (4) reporting for the purpose of Identity testing, which is unacceptable. Please remove the test for (b) (4) from the Lot Release Protocol template.

The (b) (4) test was removed from the lot release protocol template.

Product Reviewer’s Comment: The sponsor’s response to this IR is acceptable.

- G. **Proposed Drug Substance and Drug Product Specifications** (Revised list of Drug Substance Specifications was submitted in Amendment 42, received 28-SEP-2018. Revised list of Drug Product Specifications was submitted in Amendment 54, received 12-MAR-2019)

The in-process and lot release testing are performed primarily at ADMA’s Quality Control Laboratory Services Department in Boca Raton, FL (except for a few specific tests as indicated in Tables 4 and 5 below).

(b) (4)

(b) (4)

Table 5: Proposed Specifications for RI-002 Drug Product

| Test | SOP No. | DP Specification |
|---|-------------------------------------|---|
| Appearance | QC2130 Visual inspection | Clear to slightly opalescent; colorless to pale yellow; free of turbidity and visible particles |
| (b) (4) | QC3148 (b) (4) | (b) (4) |
| pH | QC2129 pH | 4.0-4.6 |
| Protein | QC2100 (b) (4) | 90-110 g/L |
| (b) (4) Purity (b) (4) | QC2161 (b) (4) | (b) (4) |
| (b) (4) Purity (Protein Composition) | QC3099 (b) (4) | ≥96% Gamma Globulin |
| Identity (Human) | QC2049 (b) (4) | Human – Positive |
| Chloride | QC2059 (b) (4) | 100-140 mM |
| Glycine | QC2105 (b) (4) | 200-290 mM |
| Polysorbate 80 | QC2255 (b) (4) | 0.15-0.25% |
| (b) (4) | QC3192 (b) (4) | (b) (4) |
| (b) (4) | QC2058 (b) (4) | (b) (4) |
| (b) (4) | LAB3013 (b) (4) | (b) (4) |
| (b) (4) | LAB3013 (b) (4) | (b) (4) |
| (b) (4) | LAB3013 (b) (4) | (b) (4) |
| Sterility | STP0081** (b) (4) | Meets 21 CFR 610.12 Requirements |
| Pyrogenicity | 16E-02 (b) (4) | Meets (b) (4) requirements at the 21 CFR 610.13 dose |
| IGIV Potency (Polio Titer) ¹ | V-7205 Neutralization (b) (4) | Type 1: (b) (4) CBER Ref Std, Lot 176 or (b) (4) CBER Ref Std, Lot 177 |
| IGIV Potency (Measles Titer) ² | V-6807 | (b) (4) CBER Ref Std Lot 176 or (b) (4) |

| | | |
|--|------------------------------------|-------------------------------|
| | Neutralization (b) (4) | (b) (4) CBER Ref Std Lot 177 |
| IGIV Potency (Diphtheria Titer) ³ | SOP-eQC-0251 (b) (4) (b) (4) | (b) (4) |
| IGIV Potency (Anti-HBs) | (b) (4) | (b) (4) CBER Ref Std, Lot 176 |
| Particulate Matter | STP0011 (b) (4) | (b) (4) |
| (b) (4) | TM-10011 (b) (4) | (b) (4) |
| (b) (4) | QC3139 (b) (4) | (b) (4) |

*(b) (4) stability evaluation required before release. Results (b) (4) after one month (b) (4) release without further evaluation Results (b) (4) after one month at (b) (4) require management review to finalize disposition

** Lots with initial test results above the specification limit are (b) (4) with independent samples in independent assay runs and investigated as per BPC's SOP for investigations to determine if any out of trend in process test results or processing conditions occurred during manufacture of the lot. If (b) (4) results have a ratio (b) (4) the average of the original result and the (b) (4) results is (b) (4), and no out of trend in process test results or processing conditions can be identified in the lot manufacturing process investigation, the lot is released.

Changes :

1. CBER Reference Standard Lot 177 is added to the test method and specification. Poliovirus types 2 and 3 specifications were removed.
2. CBER Reference Standard Lot 177 is added to the test method and specification.
3. Method SOP number was changed.

Product Reviewer's Comments: (1) The addition of the CBER Reference Standard Lot 177 for Measles and Polio testing addresses the issue of the declining stocks of CBER Reference Standard Lot 176. In response to our 11-DEC-2018 IR, the qualification data and statistical calculations were provided by the sponsor in Amendment 47 (received 26-DEC-2018).

(2) The removal of the poliovirus types 2 and 3 DP specifications is acceptable, especially since the World Health Organization (WHO) has a containment initiative to minimize the use of poliovirus type 2 in testing and research laboratories [refer to the WHO's Polio Eradication and Endgame Strategic Plan 2013-2018, WHO Global Action Plan (GAPIII)]. These DP specifications have also been removed from the lot release protocol template in response to our IR sent on 13-MAR-2019 (see Amendment 58, received 15-MAR-2019).

H. Other Assays

1. Summaries of analytical procedures for Appearance, (b) (4) Glycine, IGIV Potency (Anti-HBs), and Particulate Matter were submitted in Amendment 47 (received 26-DEC-2018) with no changes found.
2. The (b) (4) testing method was changed from (b) (4). This change was submitted previously as a Changes Being Effected in 30 Days (CBE-30) submission under Bivigam STN (b) (4). The Product Office review recommended approval of this change (see Dr. Maria Virata-Theimer's review memo dated (b) (4), however, (b) (4) on BPC at the time resulted in a Complete Response Letter being issued to the sponsor on (b) (4).
3. In response to the 08-FEB-2019 Information Request, ADMA provided the most recent version of Appearance assay SOP (version 15 of QC2130 *Visual Evaluation of (b) (4) Final Vial Products*). Compared to the version 10 submitted in the original BLA, the revised procedures detail the training of the visual inspection analysts (QC3126 *Training and Qualification of Visual Inspection Analysts*)

to use qualified commercial reference standards (QC3230 *Preparation and Qualification of Commercial Opalescence Standards*) for the determination of clarity. In addition, use of qualified standards for visual inspections will ensure analysts can accurately and consistently determine the level of clarity and opalescence in a drug product. This change is under change control CC16148 and was reported in the 2015-2016 Bivigam Annual Report STN 125389/153 (received 21-FEB-2017, review completed 26-JUL-2017).

4. For the (b) (4) assay for (b) (4) ADMA stated that initial (b) (4) testing for the clinical trial lots was performed at (b) (4) (48017.CD). The assay was transferred to (b) (4) for further optimization and validation. SOP QM4920 was listed in the original submission with validation report of KCM205-0416-ANA. SOP PDR-ATM-AHX.0001 is listed in the current submission and its validation is reported in TTP-AHX-M0004MT. Stability testing of the clinical testing post-transfer and testing of the RI-002 conformance lots manufactured by the optimized process was performed by (b) (4). Dr. Judy Beeler of OVRP/DVP/LPRVD was requested as a consult reviewer to verify if (b) (4) assay had been adequately validated. She commented that there are a few questions about the assay that still need to be addressed particularly if ADMA intends to use this test for lot release. If ADMA intends to use this test for lot release, a biostatistician should review the validation data as well. The questions and comments from Dr. Beeler (see details in her review memo dated 5-MAR-2019) will be conveyed to ADMA if/when they submit a new Investigational New Drug (IND) study for treatment of (b) (4) infections.