



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

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**To:** BLA STN 125590/0 File

**From:** Maria L. Virata-Theimer, Ph.D., Chemist, LPD/DHRR/OBRR  
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**Through:** Michael C. Kennedy, Ph.D., Team Leader, LPD/DHRR/OBRR  
Basil Golding, M.D., Division Director, DHRR/OBRR

**CC:** Yu Do, M.S., RPM, RPMS/OBRR

**Applicant:** ADMA Biologics Inc., Ramsey, NJ

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

**Subject:** CMC Review: Original BLA – (b) (4) Drug Product Specifications,  
Analytical Procedures and their Validation Studies – assigned to the Product Office

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**Recommendation**

A Complete Response (CR) letter is recommended for this Original BLA, which should include the following CR items:

1. Any reference to (b) (4) should be excluded from the labeling, promotional materials, and product release specifications. You cannot make an implicit product claim re: (b) (4) without the corresponding clinical efficacy data.
2. For the Identity testing of RI-002, you proposed to develop a method SOP which will be based on the Identity test method that 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), 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.

**Executive Summary**

This Discipline Review memorandum covers assigned CMC sections of the original Biologics License Application (BLA) submission from ADMA Biologics Inc., for Immune Globulin Intravenous (Human)(IGIV), 10% Liquid,

ASCENIV (RI-002), which was received by FDA CBER on 31-JUL-15. The CMC sections we reviewed were the (b) (4) Drug Product Specifications, Analytical Procedures and their Validation Studies that are usually assigned to the Product Office for review, which included: (b) (4) Potency-Polio, Potency-Measles, Potency-Anti-Hepatitis B surface antigen, (b) (4), Appearance, Chloride, (b) (4) Purity, Glycine, Identity, (b) (4), pH, Residual Ethanol, (b) (4). In general, most of the information provided by ADMA for these sections in the original BLA submission and in their responses to our information requests was acceptable and adequate. However, the issues concerning the (b) (4) specification and the implication of a (b) (4) disease indication claim, as well as the compliance issues at the Biotest manufacturing facility need to be resolved before this BLA can be approved.

### **Background Summary**

FDA CBER received on 31-JUL-15 this original Biologics License Application (BLA) submission from ADMA Biologics Inc., for Immune Globulin Intravenous (Human)(IGIV), 10% Liquid (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.

Pei Zhang, M.D. of LPD/DHRR/OBRR is the chair of this BLA submission. Our CMC review focused on the following assigned Drug Substance and Drug Product Specifications, Analytical Procedures and their Validation Studies: 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, (b) (4) Chloride, (b) (4) Purity, Glycine, Identity, (b) (4) (which are usually reviewed by the Product Office). We consulted Mikhail Ovanesov, Ph.D., of LH/DHRR/OBRR for issues related to the (b) (4) assay. For (b) (4) issues, we consulted Judy Beeler, M.D. of LPRV/DVP/OVRR. The other (b) (4) Drug Product Specifications, Analytical Procedures and their Validation Studies such as: (b) (4) Purity, Particulate Matter, Polysorbate 80, Potency-Diphtheria, Protein Content, Pyrogenicity, Sterility, Bioburden, and Endotoxin, were reviewed by DBSQC/OCBQ (see their (b) (4) Purity review memo dated 29-FEB-16, their Discipline Review memo dated 24-MAR-16 and Addendum Review Memo dated 14-JUL-16). LACBRP/DBSQC/OCBQ also reviewed the (b) (4) assay for in-support testing purposes (see their Review Memo dated 29-MAR-16).

### **Supplement Review Summary**

RI-002 is a sterile solution of human immunoglobulin at a protein concentration of 100 mg/mL of which  $\geq 96\%$  is IgG. It is formulated in 100-140 mM sodium chloride, 200-290 mM glycine, 0.15–0.25% polysorbate 80 at pH 4.0–4.6. The product is currently filled into 50 mL glass vials (5 g/50 mL, target volume of (b) (4) mL). RI-002 is manufactured from large pools of human Source Plasma (SP) (total pool volumes of (b) (4) units collected from normal, non-immunized donors) according to a modified Cohn-Oncley cold alcohol fractionation process and with two added viral inactivation steps (solvent/detergent treatment with Triton X-100 and tri-n-butyl phosphate (b) (4) filtration using a 35 nm filter). The starting material (plasma pool) actually consists of plasma from normal SP donors (b) (4).

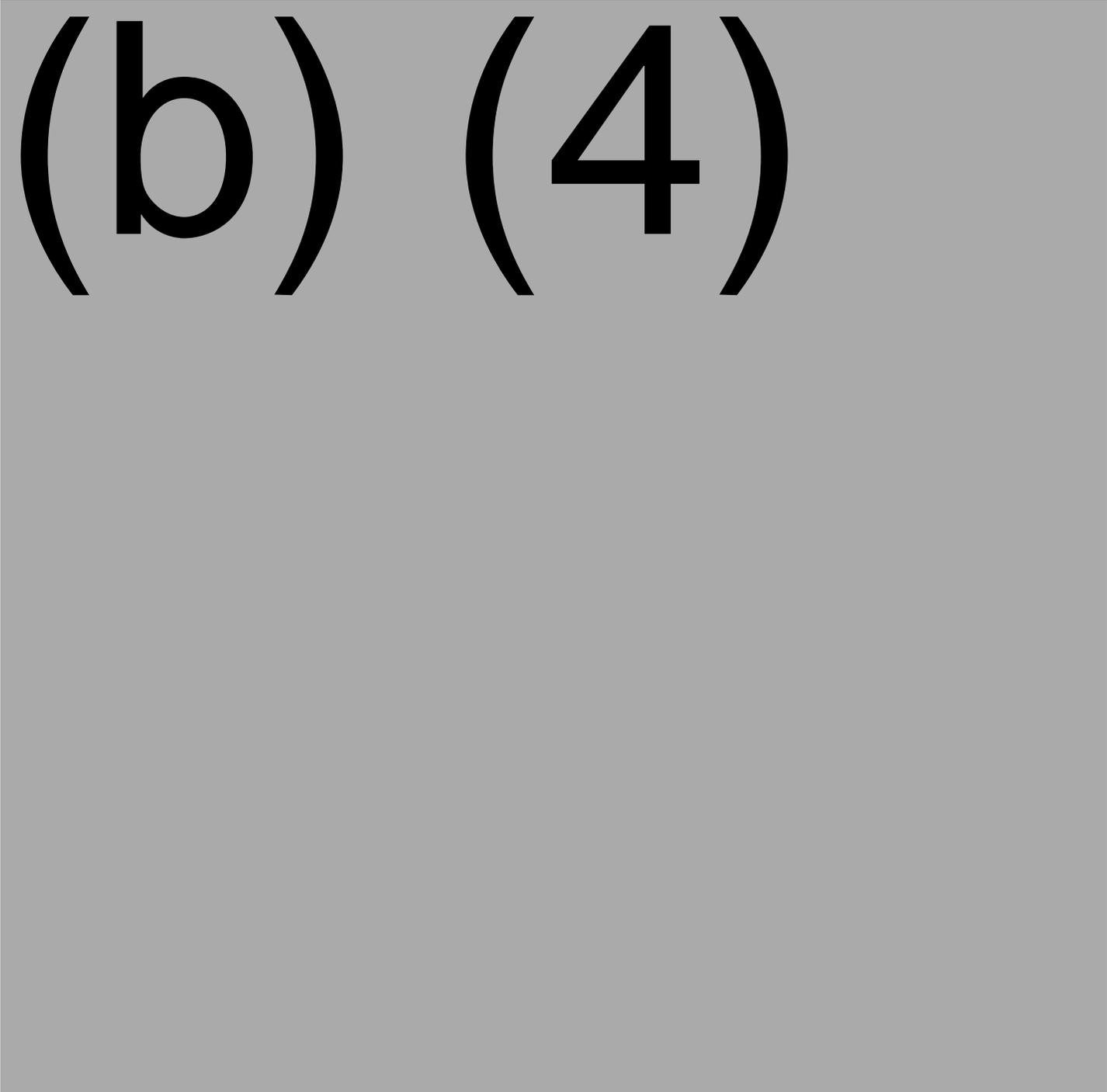
The proposed shelf life of RI-002 is 24 months, stored at 2-8 °C.

Manufacture, in-process and most of the lot release testing of RI-002 are performed at a contract manufacturer, the Biotest Pharmaceutical Corporation (BPC) facility in Boca Raton, FL. Filling into final container vials is performed at (b) (4).

***Product Reviewers' Comments:*** In the Original BLA submission (Section 3.2.S.2.3 Control of Materials, Part 3.2.6.2 RSV Donor Program Testing), the sponsor did not provide much detail on how the RSV program donors were being screened for neutralizing anti-RSV antibodies (e.g., definition of "sufficient" RSV neutralizing titer to qualify for the RSV donor program, dilutions, acceptable titer cut-offs). In addition, the sponsor did not state the proportion of plasma from the RSV donor program that is (b) (4) plasma.

I. Proposed (b) (4) Drug Product Specifications, Analytical Procedures and their Validation Studies

We compared the proposed (b) (4) Drug Product (DP) specifications of RI-002 with those of BPC's licensed IGIV product, Bivigam™, which is also a 10% protein solution and manufactured similarly (BLA STN 125389 Current files in EDR: (b) (4) of 18-DEC-15, DP as of 12-SEP-14). As mentioned previously, in-process and lot release testing are performed primarily at the BPC Quality Control Laboratory Services Department in Boca Raton (except for a few specific tests as indicated in Tables 1 and 2 below).



**Table 2: Proposed Specifications for RI-002 Drug Product compared to those of Bivigam Drug Product**

Test	SOP No.	Bivigam	RI-002
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<b>Appearance</b>	QC2130 Visual inspection	Clear to slightly opalescent liquid; colorless to pale yellow; free of turbidity	Clear to slightly opalescent liquid; colorless to pale yellow; free of turbidity and visible particles
(b) (4)	QC3148 (b) (4)	(b) (4)	(b) (4)
<b>pH</b>	QC2129 pH	4.0-4.6	4.0-4.6
<b>Protein</b>	QC2100 (b) (4)	90-110 g/L	90-110 g/L
(b) (4)	QC2161 (b) (4)	(b) (4)	(b) (4)
<b>Purity (Molecular Profile)</b>			
(b) (4) <b>Purity (Protein Composition)</b>	QC3099 (b) (4)	≥96% Gamma Globulin	≥96% Gamma Globulin
<b>Identity (Human)*</b>	QC2049 (b) (4)	Human - Positive	(Human – Positive)*
<b>Chloride</b>	QC2059 (b) (4)	100-140 mM	100-140 mM
<b>Glycine</b>	QC2105 (b) (4)	200-290 mM	200-290 mM
<b>Polysorbate 80</b>	QC2255 (b) (4)	0.15-0.25%	0.15-0.25%

(b) (4)

<b>Sterility</b>	STP0077 or STP0081** STP0077*** (b) (4)	Meets 21 CFR 610.12 Requirements	Meets 21 CFR 610.12 Requirements
<b>Pyrogenicity</b>	(b) (4)	Meets (b) (4) requirements at the 21 CFR 610.13 dose	Meets (b) (4) requirements at the 21 CFR 610.13 dose
<b>IGIV Potency (Polio Titer)</b>	V-5355/04-09 Neutralization (b) (4)	(b) (4)	Type 1: (b) (4) CBER Ref Std, Lot 176 OR Type 2: (b) (4) CBER Ref Std, Lot 176 OR Type 3: (b) (4) CBER Ref Std, Lot 176
<b>IGIV Potency (Measles Titer)</b>	V-6807/01-10 Neutralization (b) (4)	(b) (4) CBER Ref Std Lot 176	(b) (4) CBER Ref Std Lot 176
<b>IGIV Potency (Diphtheria Titer)</b>	QM/1143/01 (b) (4)	(b) (4)	(b) (4)
<b>IGIV Potency (Anti-HBs)</b>	QC3014 (b) (4)	(b) (4) CBER Ref Std, Lot 176	(b) (4) CBER Ref Std, Lot 176

Particulate Matter	STP0011 (b) (4)	(b) (4)	(b) (4)
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(b) (4)

For (b) (4) (first specification): Lots with initial test results above the specification limit are retested (b) (4) times 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 both the retest results have a ratio (b) (4), the average of the original result and the (b) (4) retest 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.

For (b) (4) (second specification): Lots with alert limit results are retested (b) (4) times with independent samples in independent assay runs. If both of the retest results have a ratio of (b) (4) and the average of the original result and the two retest results is (b) (4), the lot is released.

*\*CBER requested the sponsor to change their identity test (and specification) in order to distinguish RI-002 from the Biotest immune globulin products being tested in the same QC laboratory (see Product Reviewers' Comments and Response to 13-APR-16 Late Cycle Meeting Comments below)*

*\*\* Bivigam only*

*\*\*\*RI-002 only*

*\*\*\*\*ALC = Alert Limit Control (proposed as of BLA Amendment 21, received 29-JAN-16)*

*\*\*\*\*\*CBER requested the sponsor to remove the (b) (4) specification and any mention of (b) (4) from the package insert (see Product Reviewers' Comments and Responses to 11-JAN-16 Information Request below).*

**Product Reviewers' Comments (on the Analytical Methods and Specifications assigned to the Product Office as well as on the CMC-related sections in the proposed package insert):**

1. Testing laboratories: Except for (b) (4) testing), all the testing laboratories for RI-002 and Bivigam appear to be the same.
2. Product specifications, method SOPs and method validation studies in general: RI-002 and Bivigam have similar specifications for (b) (4) DP, which are mostly acceptable due to their similar manufacturing process and formulation. ADMA also referenced most of Biotest's previously approved method SOPs and submitted the most updated versions in this BLA as well as their previously reviewed method validation reports. The only notable difference between the two products was the (b) (4) proposed for RI-002. We also requested that they change their proposed Identity test method and specification in order to comply with 21 CFR 610.14 requirements (see more details in no. 10 below).

3. (b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

4. Total IgA method – ADMA currently lists BPC’s (b) (4) test method for the testing total IgA in RI-002, however, BPC plans to change their test method from (b) (4) to (b) (4) test kits and reagents (CBE-30 STN (b) (4), received 21-DEC-15, recommended for approval, but was issued a CR Letter on 16-JUN-16 due to a compliance hold on BPC). The Total IgA specification will remain the same.
5. Anti-Polio test method validation: (b) (4) test method will be used to detect anti-polio antibodies (SOP V-5355/04-09, effective 02-MAR-09). Testing will be performed by the (b) (4) (b) (4), Centre for Infections Virus Reference Department). They list potency specifications for each of the three known polio types, although having a specification for at least one type is already sufficient [21 CFR § 640.104b(3)]. ADMA did not provide (b) (4) method validation report and erroneously stated the following: “As this is performed by the (b) (4) no validation is required.” (see Section 2.3.P.5 Drug Product, subsection 5.18 Polio by Neutralization). An IR was sent to the sponsor on 08-JAN-16 to request for this missing report (see Responses to the 08-JAN-16 IR below).
6. (b) (4) test method and specification: Dr. Ovanosov identified several issues with BPC’s (b) (4) assay and the proposed specification that need clarification and even revision. Three reference

standards were listed throughout different sections related to this assay. The proposed specification states that use of an internal standard (an internal lot) where it is preferable to use an international reference standard as the basis for calculating the (b) (4). An IR was sent to the sponsor on 8-JAN-16 to clarify these issues (see Responses to the 08-JAN-16 IR below).

7. Endotoxin test method: The sponsor submitted two method SOPs re: the endotoxin test in the Original BLA submission. An IR was sent to the sponsor on 08-JAN-16 to seek clarification about these two submitted method SOPs (see Responses to the 08-JAN-16 IR below).
8. (b) (4)
9. (b) (4)
10. Identity test method and specification: For identity testing of RI-002, ADMA proposed to use the same test method [SOP QC2049 – an (b) (4) method to detect human serum proteins (globulins)] and specification (“Human – positive”) that BPC has used for identity testing of their immune globulin products, Bivigam and Nabi-HB®. RI-002 and the other BPC products will be tested for identity in the same BPC QC test laboratory. This proposal is not in accord with the applicable regulation, 21 CFR 610.14. The Identity test requirements in 21 CFR 610.14 state that, “*the contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on the final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory.*”

The SOP QC2049 was erroneously listed as an (b) (4) method in the Drug Product Specifications list that was submitted. In SOP QC2049, no (b) (4) is applied to the (b) (4), therefore it is not an (b) (4) method, but rather a (b) (4) reaction that takes place in a (b) (4).

Due to the timing of the Late-Cycle Meeting (LCM), the sponsor was alerted about this issue via the LCM materials package that was sent on 1-APR-16. During the LCM discussion on 13-APR-16, ADMA was made aware of FDA’s expectations that the RI-002 material itself should be tested for identity and was asked to submit a proposal to use other methods (physical, chemical, immunological) to ensure that the IgG of RI-002 can be distinguished from the other BPC products (e.g., Nabi-HB) being tested for identity in the same BPC QC test laboratory. FDA told ADMA that using different colored caps on the vials was not sufficient (see ADMA’s Response to 13-APR-16 LCM below)

11. Proposed use of (b) (4) filter (package insert): An IR was sent to the sponsor on 11-JAN-16 to request that they remove the statement in the package insert pertaining to the use of an (b) (4) filter (see Responses to the 08-JAN-16 IR below).

## II. Responses to Information Requests

After initial review, two sets of Information Requests were sent to ADMA on 08-JAN-16 and 11-JAN-16. Responses from the firm were received on 29-JAN-16 (see BLA Amendment 21, STN 125590/0.21), on 03-FEB-16 (see BLA Amendment 22, STN 125590/0.22), on 11-FEB-16 (see BLA Amendment 24, STN 125590/0.24) and on 29-APR-16 (see BLA Amendment 33, STN 125590/0.33). Comments were also conveyed during the 13-APR-16 Late-Cycle Meeting to which the sponsor responded to (see BLA Amendment 34, STN 125590/0.34, received 9-MAY-16). ADMA’s responses are summarized below:

**A. Responses to the 08-JAN-16 Information Request (received on 29-JAN-16 in BLA Amendment 21, received on 11-FEB-16 in BLA Amendment 24, received on 29-APR-16, in BLA Amendment 33)**

1. In various sections of the BLA pertaining to the (b) (4) assay, you listed three different reference standards for calibration or qualification purposes, e.g., (b) (4) Reference Standard, (b) (4) reference material (b) (4) and FDA's (b) (4) standard. Please clarify which reference standard will be the sole basis for calculating the (b) (4) of the final drug product. In addition, for the chosen reference standard, please provide the following supporting information:

a. A detailed description of the reference standard, including its source, reported (b) (4), preparation and storage conditions

The sponsor stated that the (b) (4) is determined in (b) (4) using (b) (4) reference standard (b) (4) sourced from (b) (4) and qualified by (b) (4)

(b) (4)

b. The qualification study report for the use of the reference standard

(b) (4) was qualified by (b) (4) against the (b) (4) reference reagent (b) (4) according to protocol PR-10028-4 with a result of (b) (4) confidence interval: (b) (4)

*Product Reviewers' Comment:* The sponsor provided the certificate of analysis for (b) (4) in Amendment 21 and again in Amendment 24.

c. Stability data

(b) (4) is formulated by (b) (4) in a proprietary buffer and stored at (b) (4) qualifies the material activity prior to use. The sponsor submitted stability results for (b) (4) for the initial and (b) (4) time points in Amendment 21, while the (b) (4) time point data, which was performed under an updated protocol, PR-10028-5, was submitted later in Amendment 24. At each time point, 3 vials of (b) (4) were tested for potency by the (b) (4) assay (SOP TM-10011) by (b) (4). The acceptance criterion was set at (b) (4)

(b) (4)

(b) (4)

*Product Reviewers' Comment:* The stability results so far have met the acceptance criteria and show that the (b) (4) lot is still potent after (b) (4) months of storage at (b) (4). According to the submitted protocol, PR-10028-5, the vials stored at (b) (4) are to be assessed at (b) (4). The submitted information appears to be adequate and acceptable.

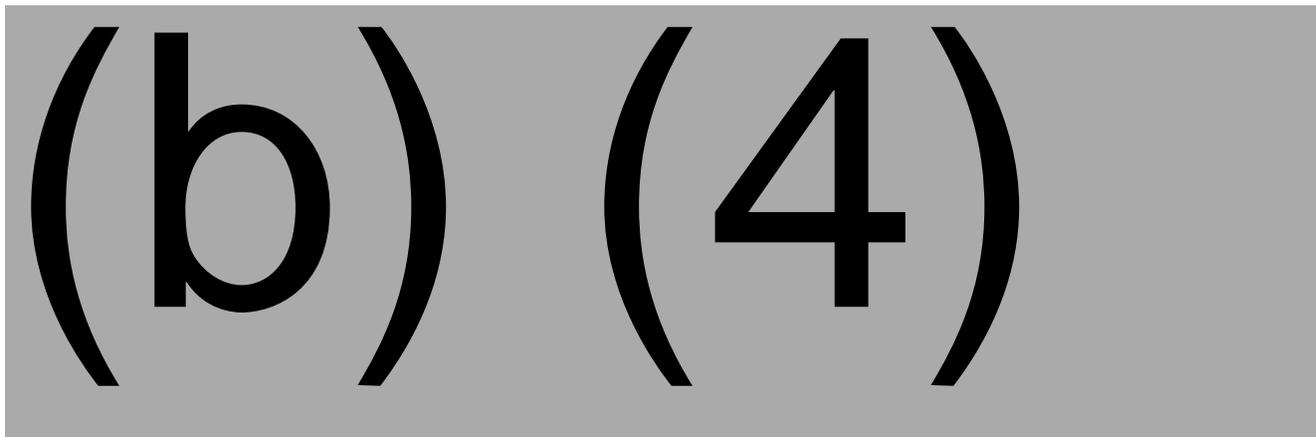
2. **To prevent further confusion, we suggest that you revise the wording of your (b) (4) Drug Product Specification to indicate which reference standard you will be using as the basis for calculating the (b) (4) (i.e., not the internal standard).**

(b) (4) is reported as a ratio to a qualified alert level control (ALC), which has been qualified against lot (b) (4) provided by FDA to BPC for the development of the (b) (4) Assay.

The current ALC is Lot (b) (4) of Bivigam (b) (4), which has (b) (4) protein concentration and formulation as Bivigam and RI-002 drug product. The material is subdivided into aliquots and stored (b) (4). The material was initially qualified in 2013 (*Report no. 20130816-1 Identification and Qualification of an Initial ALC for IGIV (b) (4) Assay*) and is requalified (b) (4) according to protocol PR-10015 (*Requalification of an ALC for Bivigam*). The activity of ALC Lot (b) (4) reported in the 2015 requalification is (b) (4) (*see submitted Report no. 20150624-1 Requalification of the ALC for IGIV (b) (4) Assay, dated 24-JUN-15*).

The material is trended against the historic activity of the (b) (4) standard (specification (b) (4) standard)<sup>1</sup> and the 95% confidence interval of the line cannot cross the lower limit for (b) (4) (<sup>1</sup>Note: Since RI-002 and Bivigam are formulated at 10% protein and (b) (4) was formulated at (b) (4) protein, the activity of (b) (4) was adjusted by a factor of (b) (4) for the comparison). Also, the linear regression of activity over time does not show a significant slope. Lot (b) (4) met these criteria during the 2015 requalification.

The performance of the ALC ratio as the specification for (b) (4) was evaluated and approved for continued use in report FR-2015-05 which analyzed (b) (4) lots of Bivigam manufactured from June 2014 to February 2015. ADMA commits to revising the specification to clarify which standard is used for the ratio calculation. The proposed change is in Table 4 below:



3. **With regard to Questions 1 and 2, please revise the appropriate sections of the BLA accordingly to clarify which reference standard you will use to calculate the (b) (4).**

Sections 3.2.P.6, 3.2.P.5.2.20, 3.2.P.5.3.20 and 3.2.P.5.6.20 have been revised to clarify which reference standard is used to calculate (b) (4).

4. **In order to ensure that the formulation of your final product does not affect the (b) (4) assay results, please perform additional (b) (4) testing of the final product using (b) (4) methods and compare the outcomes, if possible. You may use assays that are commercially available, e.g., a (b) (4) assay.**

IR Response in BLA Amendment 21: The (b) (4) Assay, as currently performed, includes (b) (4)

as RI-002. The reportable result is a relative potency measurement (b) (4)

Any matrix effect that may exist with the sample would be the same as that

exhibited by the ALC. Thus reporting a ratio mitigates matrix effect on results for the (b) (4) specification. To further address the possibility of matrix effects, an (b) (4) assay is being qualified. Once qualified, a separate study comparing the RI-002 (b) (4) results from both assays will be performed. ADMA expects to have the data for submission by 30-APR-16.

IR Response in BLA Amendment 33:

**Consult Reviewer's General Comments re: IR Response in BLA Amendment 21** (from Dr. Ovanesov's email dated 29-JAN-16): I briefly read through the responses to questions 1-4 (the (b) (4) questions). The responses and submitted data are acceptable and reasonable. The company was performing their testing using the appropriately calibrated standards. This information was missing from the original submission but the omissions were corrected as needed.

**Consult Reviewer's General Comments re: IR Response in BLA Amendment 33** (from Dr. Ovanesov's emails dated 17-MAY-16): They failed the (b) (4) study. (b) (4) and (b) (4) assays do not agree. They acknowledged that they do not know what is happening there. Probably matrix effects and may be other impurities. Their response is not acceptable. They failed and proposed no CAPAs and no further investigations. The company has to investigate the root causes for the discrepancy. They need to study more batches and answer the following questions: "Are we missing any potential (b) (4) impurities?", If the matrix effect is strong, should we use the (b) (4) method at all?"

The qualification report for the (b) (4) assay is acceptable which leaves us with the hypothesis that, since the two assays gave drastically different results, the (b) (4) test validation was deficient. They claim that matrix effects or additional impurities are responsible for the discrepancy. This raises a question: was the (b) (4) method properly qualified per the ICH guidelines? Both issues should have been revealed during (b) (4) method validation.

By the way, I do not think this is a CR issue per se, but there are two regulatory issues that need to be addressed either pre-ADD or as a PMC: 1. Deficient validation of (b) (4) method and related deficiency in specifications. 2. Deficient characterization of (b) (4) impurities in the product (impact of manufacturing consistency should be studied as well).

**Product Reviewers' Comment:** More IR questions regarding the (b) (4) assay were sent by the DBSQC reviewers on 8-MAR-16. ADMA's responses to these questions can be found in BLA Amendment 30 (received on 22-MAR-16) which were reviewed by DBSQC). As of the writing of the review memo, DBSQC reviewers still had issues regarding robustness studies that were performed. Some of their issues overlap with Dr. Ovanesov's concerns.

**5. Please provide the method validation report from (b) (4) regarding their Polio neutralization assay.**

The Virus Reference Department at the (b) (4) contains WHO accredited national laboratories for poliovirus; however, a formal validation is unavailable. In addition, laboratory trending data supports assay control. The laboratory that performs the polio assay includes appropriate controls for assay performance and includes CBER Lots 176 or 177 in all assays for RI-002. The polio neutralization testing assay has acceptable pass/fail rates as reported in Table 5 below:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

ADMA committed to continual improvement of the polio neutralization assay. A project has been initiated to perform the assay in a qualified BPC laboratory. The assay will be developed and validated to meet the requirements of the ICH Q2(R1) guidelines and the FDA *Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics*. This will include appropriate qualification of BPC data against the current reported data. The expected completion date of this project is the 4<sup>th</sup> Quarter of 2017.

ADMA will perform the required evaluation and acceptance activities, such as auditing of the facility and validation documents prior to transfer to the BPC laboratory. In the interim, the performance of the CBER standard will continue to be trended for acceptable assay performance.

*Product Reviewers' Comment: The sponsor's responses are adequate and acceptable.*

6. **Endotoxin test: Two SOPs, QC2147 and QC3121, are listed under 2.3.R Regional Information and 3.2.R Regional Information. Only QC2147 is listed under 2.3.S Control of (b) (4) 3.2.S.4.1 Specification, 2.3.P Control of Drug Product and 3.2.P.5.1 Specifications.**

- a. **Please indicate which SOP was used in your process validation.**

ADMA stated that endotoxin is only tested during the (b) (4) stage. SOP QC3121 was used in the process validation of all (b) (4) lots. Step (b) (4) of SOP QC3121 references SOP QC2147 for details of individual sample preparation.

- b. **Please clarify which SOP corresponds to the validation report VP-FR-3558.**

SOP QC3121 corresponds to validation report VP-FR-3558.

- c. **What is the difference between QC2147 and QC3121?**

SOP QC3121 details the procedure used for (b) (4) test method for detection of bacterial endotoxin. SOP QC2147 details the procedure for individual sample preparation. Section 3.2.S.4.3.4 has been revised to clarify the difference between the two procedures.

*Product Reviewers' Comment: The sponsor's responses are adequate and acceptable.*

7. **(b) (4) test: Two SOPs, QC3192 and QC2194, are listed under 2.3.R Regional Information and 3.2.R Regional Information. Only QC3192 is listed under 2.3.S Control of Drug Substance, 3.2.S.4.1 Specification, 2.3.P Control of Drug Product and 3.2.P.5.1 Specifications.**

- a. **Please indicate which SOP was used in your process validation.**

SOP QC2194 was used in the process validation of all (b) (4) clinical/conformance lots for RI-002. SOP QC3192 will be used for commercial lots.

- b. **Do you intend to use both SOPs for your Drug Substance and Drug Product lot testing? If yes, please indicate which SOP will be the primary method.**

SOP QC3192 will be the only method used for DS and DP lot testing. In response to FDA's notification that (b) (4)

(b) (4) SOP QC3192 employs the same basic principles as SOP QC2194.

*Product Reviewers' Comment: The sponsor's responses are adequate and acceptable.*

8. **(b) (4) test: Two SOPs, QC3178 and T:EA-148-02, are listed under 2.3.R Regional Information and 3.2.R Regional Information. Only QC3178 is listed under 2.3.S Control of Drug Substance, and 3.2.S.4.1 Specification.**

- a. **Please indicate which SOP was used in your process validation.**

SOP T:EA-148-02 was performed at Biotest AG for DS lots (b) (4). SOP QC3178 was performed at BPC Boca Raton for DS lots (b) (4).

- b. Do you intend to use both SOPs for your (b) (4) lot testing? If yes, please indicate which SOP will be the primary method.

SOP QC3178 will be the only method used for future (b) (4) lot testing. However, both procedures are performed under the principle that the (b) (4)

*Product Reviewers' Comment: The sponsor's responses are adequate and acceptable.*

9. (b) (4): Two SOPs, QC3177 and T:EA-139-02, are listed under 2.3.R Regional Information and 3.2.R Regional Information. Only QC3177 is listed under 2.3.S Control of Drug Substance, and 3.2.S.4.1 Specification.

- a. Please indicate which SOP was used in your process validation.

SOP T:EA-139-02 was performed at Biotest AG for process validation of DS lots (b) (4). SOP QC3177 was performed at BPC Boca Raton for process validation of DS lots (b) (4).

- b. Do you intend to use both SOPs for your Drug Substance lot testing? If yes, please indicate which SOP will be the primary method.

SOP QC3177 will be the only method used for future DS lot testing. However, both procedures are performed under the principle that in the first step of the assay, (b) (4)

*Product Reviewers' Comment: The sponsor's responses are adequate and acceptable.*

**B. Responses to the 11-JAN-16 Information Request (received on 3-FEB-16 in BLA Amendment 22)**

1. Since this BLA is for a Primary Humoral Immunodeficiency indication (not for a (b) (4)-related indication), please remove any mention of (b) (4) from the Package Insert as well as from the Drug Product release specifications.

The sponsor insisted on maintaining their (b) (4) specification and the presence of (b) (4) in the package insert. To justify these, they provided additional (b) (4) documents (see BLA Amendment 22).

*Product Reviewers' Comment: We deferred to the expertise of the Clinical Reviewer (Dr. Charles Maplethorpe), the Pharm-Tox Reviewer (Dr. Evi Struble), and the Consult Reviewer (b) (4) expert (Dr. Judy Beeler of DVP/OVRR) in reviewing the (b) (4)-related supporting documents.*

*Clinical Reviewer's Comments (from Dr. Charles Maplethorpe's emails dated 4-FEB-16):*

(1) The submitted data do not permit evaluation of the extent to which (b) (4) in the investigational Immune Globulin product may have contributed to safety or efficacy outcomes.

(2) There is no compelling reason why this immune globulin product should be co-developed as a (b) (4) hyperimmune globulin product in the absence of submitted safety and efficacy data in the target population in which a (b) (4) hyperimmune product would be used.

(3) Licensure of (b) (4) hyperimmune globulin products requires demonstration of clinical benefit in the target population, and is not based on surrogate endpoint outcomes.

(4) If the intermediate goal is to make this investigational product available to treat or prevent (b) (4) this can be done using the provisions given in 21 CFR 312.

(5) Promotional claims for the use of this product to treat or prevent (b) (4) would require licensure for this indication.

**Pharmacology/Toxicology Reviewer's Comments** (from Dr. Evi Struble's email dated 4-FEB-16): I agree with Dr. Maplethorpe's responses and have no further comments. The animal data submitted cannot support a label claim absent clinical data demonstrating efficacy in the target population.

**CMC Team Leader's Comments** (from Dr. Michael Kennedy's email dated 4-FEB-16): I would like to raise the issue that this product, if licensed, will be licensed for PID and because of this is likely to be used with other IGIVs that do not have (b) (4) disease. I think this may add additional levels of risk for this product which the sponsor has not addressed. I do not support this firm being able to retain the (b) (4) claims or (b) (4) specifications.

Dr. Judy Beeler of LPRV/DVP/OVRR was consulted after the Responses to the 11-JAN-16 IR were received. She reviewed all the submitted documents related to the (b) (4) test to date and compared the RI-002 data to that of (b) (4). She found the method validation data and (b) (4) study data provided by the sponsor to be insufficient to support labeling the product for prevention or treatment of (b) (4) in immunodeficient patients (see her Consult Review Memo dated 18-MAY-16).

This (b) (4) issue was included in the Late-Cycle Meeting (LCM) materials package that was sent to the sponsor on 1-APR-16. During the LCM on 13-APR-16, FDA suggested that a separate meeting is needed to discuss the (b) (4) issues. The sponsor requested a face-to-face conference with FDA, which took place on 27-JUN-16 (see 27-JUN-16 Meeting Summary in the BLA file). As of the writing of this review memo, FDA maintains that any mention of (b) (4) should be removed from the labeling and the product release specifications until ADMA can provide the supporting clinical efficacy data.

2. **As stated before during the October 7, 2014 pre-BLA Type B Meeting, FDA discourages the use of in-line filters as these do not necessarily prevent particulates from going through or from reforming after filtration. Please remove any mention of using an (b) (4) filter from the Package Insert.**

ADMA Biologics Inc. commits to removing the reference for the use of (b) (4) filter during the RI-002 administration. The package insert will be updated to reflect this commitment with the next revision submitted for Agency review.

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

## C. Response to 13-APR-16 Late Cycle Meeting Comments (Identity Test)

### 1. Proposed Identity Test for RI-002

ADMA proposes to use the significant difference in anti-HBs levels between Nabi-HB and RI-002 as evidence of the correct identity of the RI-002 final package product. RI-002 has an anti-HBs potency release specification of (b) (4), while Nabi-HB, which contains high levels of anti-HBs antibodies, has an anti-HBs potency release specification of (b) (4). Both products are tested for anti-HBs using the same method SOP QC3014 (which uses the (b) (4)), however, each lot of Nabi-HB generates over (b) (4) times more anti-HBs signal than any RI-002 lot.

For identity testing of Nabi-HB, BPC uses method SOP LAB3014 (Hepatitis B Immune Globulin Identification Procedure for Final Container using the (b) (4) ) which was based on the SOP QC3014, where the high anti-HBs signal generated by Nabi-HB is used as the identification of the Nabi-HB product. This method uses the same instrumentation, reagents and test principles as QC3014. Rather than determining anti-HBs potency, LAB3014 was developed to differentiate Nabi-HB from normal immunoglobulin by means of a positive or negative result. A dilution of (b) (4) is used for the Nabi-HB test article. Human immune globulin is used as the negative control. Results are reported as positive or negative, with positive indicating the identity of the test sample is Nabi-HB.

ADMA proposes to apply the same principle for the development of the RI-002 final container identity test with the specification of negative to indicate that the identity of the test sample is RI-002. ADMA intends to validate the assay per ICH Q2(R1) guidelines for identity tests. Assay controls and standards will be consistent with those used in LAB3014, using Nabi-HB as a positive control.

**Product Reviewer's Comments:** (1) ICH Q2(R1), Section 1.1 Identification states the following: "The discrimination of a procedure may be confirmed by obtaining positive results (perhaps by comparison with a known reference material) from samples containing the analyte, coupled with negative results from samples which do not contain the analyte. In addition, the identification test may be applied to materials structurally similar to or closely related to the analyte to confirm that a positive response is not obtained."

*Both RI-002 and Nabi-HB contain the "analyte", i.e., the anti-HBs antibodies. They only differ by the amount of anti-HBs. Ideally [if by ICH Q2(R1)], the test sample to be identified by the identity test is expected to be the sample that shows the positive response rather than negative. In the case of RI-002, RI-002 will be identified as such if the test sample tests negative in their anti-HBs-based identity test. If the test sample tests positive, it will be identified as Nabi-HB.*

*At the moment, ADMA has only described their proposal for the RI-002 identity test, which will be designed similarly to that for Nabi-HB (SOP LAB3014) and based only on the anti-HBs content. We are not certain if this is an acceptable method or not until ADMA provides the actual method SOP for identity testing of RI-002 (with details on which positive and negative controls will be used, how the dilutions will be prepared, what titer cut-off will be applied, etc), performs a method validation study and provides the results. We will request that they provide the abovementioned items.*

(2) Some notes from LAB3014: the Nabi-HB final container lots are manually (b) (4) and then further (b) (4) by the (b) (4) during testing (b) (4). On the other hand, the external negative controls [the (b) (4) ) and an Immune Globulin final container lot] are undiluted when tested (Table 1, LAB3014). Meanwhile the external positive control (a WHO traceable Anti-HBs Control) are manually (b) (4) prior to the (b) (4) and (b) (4) for a final (b) (4) respectively.

(3) Some notes from QC3014: the validated range of the anti-HBs assay is (b) (4). All Nabi-HB samples and external positive control must be diluted into the validated range using (b) (4). In QC3014, all Nabi-HB and IGIV (b) (4) drug product samples are manually (b) (4) prior to loading on to the (b) (4). The instrument further (b) (4) test samples (b) (4).

## APPENDIX

### Supporting Documents in the Original BLA Submission that were reviewed:

1. 2.3.S Drug Substance
2. 2.3.P Drug Product
3. 3.2.S.4.1 Specification
4. 3.2.S.4.2 Analytical Procedures
5. 3.2.S.4.3 Validation of Analytical Procedures
6. 3.2.S.4.5 Justification of Specifications
7. 3.2.S.5 Reference Standards or Materials
8. 3.2.P.1 Description and Composition of the Drug Product
9. 3.2.P.5 Control of the Drug Product
10. 3.2.P.5.1 Specifications – 1.1 Drug Product Release Specifications, Table 1 Control Release Specifications Testing Unlabeled Vial
11. 3.2.P.5.2 Analytical Procedures: 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, (b) (4), Chloride, (b) (4), Purity, Glycine, Identity, (b) (4) and pH
12. 3.2.P.5.3 Validation of Analytical Procedures: Appearance, pH, (b) (4), Residual Triton X-100, Residual Tri-n-Butyl, Phosphate, Residual Ethanol, (b) (4), Potency-Polio, Potency-Measles, Potency-Anti-Hepatitis B surface antigen, (b) (4), Chloride, (b) (4), Purity, Glycine, Identity, (b) (4), and pH
13. SOP T-EA-139-02/01 Determination of (b) (4) 9-DEC-11, Biotest-AG)
14. SOP QC3177: Determination of (b) (4)
15. SOP QC3178: Determination of (b) (4)
16. SOP T-EA-148-02/00: Determination of (b) (4) in Bivigam drug product (b) (4) with (b) (4), Biotest-AG)
17. SOP QC3146: Determination of Residual (b) (4) Concentration of IGIV Product by (b) (4)
18. SOP QC3148: Determining the Presence of (b) (4) in IGIV Product by (b) (4)
19. SOP LAB3013: Determination of (b) (4)
20. SOP QC2058: (b) (4) Assay (Rev. 15)
21. SOP QC2130 Visual Evaluation of IgG (b) (4) and Final Fill Products (Rev. 10)
22. SOP QC2059: Procedure for Determination of Chloride in Immune Globulin Preparations Using (b) (4)
23. SOP QC3099: Determination of Protein Composition and Purity in Human IgG Products using (b) (4)
24. SOP QC2105: Determination of Glycine Concentration in Aqueous Samples by (b) (4)
25. SOP QC2049: Identity Test Procedure for the Detection of Human Serum Proteins in IGIV and Nabi-HB Product Samples (Rev. 3)
26. SOP QC3139: Determination of (b) (4) for Final Product Samples and Raw Materials (Rev. 6)
27. SOP STP0011: (b) (4) Particulate Matter (Rev. 7, effective 6-AUG-09)
28. SOP QC2129: pH Testing of Human IgG Products, Monoclonal Antibody (MAb) Products, and Buffer Samples (Rev. 8)
29. SOP QC3014: Anti-HBs Potency (b) (4)
30. SOP QM/1143/03: Diphtheria Antitoxin Assay (BPC)(effective 05-AUG-13)(b) (4)
31. SOP V-6807/01-10 (b) (4) Assay for Measles Antibodies – Modified SOP for Testing Immunoglobulins from Biotest Pharmaceuticals Corporation (effective 15-JUN-10)(HPA)

32. SOP QC3154: Calculation Method of Polio by Neutralization Results from Contract Lab (Rev. 3)
33. SOP QC3192: Determination of (b) (4) Activity Using the (b) (4)
34. SOP QC2106: Determination of Triton X-100 Concentration in Aqueous Samples by (b) (4)
35. SOP QC2111: Determination of TNBP in Aqueous Samples by (b) (4)
36. SOP QC3193: Determination of Residual Alcohol in IgG (b) (4) Samples by (b) (4)
37. SOP L270: Measurement of Residual and Total Alcohol by (b) (4)
38. SOP QC2267 Determination of Total IgA (b) (4) Using (b) (4)
39. TM-10011: (b) (4) Assay test Method for Biotest Pharmaceuticals Immune Globulin Drug Product (Rev. 9, implemented 17-NOV-14)(b) (4)
40. SOP V-5355/04-09: (b) (4) Test for the Detection of Poliovirus Antibodies (effective 02-MAR-09)
41. SOP QM4920.01: (b) (4) for ADMA Biologics (approved 24-JUL-15, (b) (4))
42. Technical Report: TEC-15-004-RPT-1: Comparison of (b) (4) results from (b) (4) and (b) (4)
43. Technical Report: TEC-15-005-RPT: Statistical analysis of RI-002 Clinical Trial Material (b) (4) Potency Results (approved 10-JUL-15)
44. 3.2.P.5.3.4 Validation of Analytical Procedures: (b) (4) Assay
45. Technical Report: TEC-10-001-RPT: Results of Bridging Analysis of LQC, MQC and HQC (b) (4) Assay (approved 5-OCT-10)
46. Validation Report # 5251 (b) (4) Assay (initiated 19-JUN-08, approved 4-MAR-09, (b) (4))
47. 00-V022-97 Method Validation Protocol for (b) (4) Assay (approved 1-DEC-97)
48. VP-FR-00-V022-97-1 Addendum to Method Validation for (b) (4) Assay (approved 30-NOV-09)
49. VP-FR-0422 Assay Transfer Protocol Final Report for the (b) (4) Assay (effective 22-MAR-00)
50. VP-FR-0422-2: (b) (4) Equivalency for Determination of (b) (4) in Immune Globulin (effective 12-SEP-03)
51. VP-FR-0422-3: Assay Relocation Qualification for Determination of (b) (4) in Immune Globulin (approved 14-JUN-04)
52. VP-FR-0422-4: Precision Validation for the (b) (4) Assay (2009)
53. 00-V003-98 Determination of (b) (4) in Formulated Immune Globulins (dated 31-AUG-98 and 9-SEP-98)
54. VP-FR-0383 Assay Transfer Protocol Final Report for the (b) (4) Assay (effective 2-MAR-99)
55. VP-FR-0383-4 Assay Reagent Stability Evaluation for Determination of (b) (4) in Aqueous Samples (approved 31-MAR-10)
56. VP-FR-0383-5 Addendum to Method Validation for (b) (4) in Formulated Immune Globulins (approved 3-FEB-10)
57. VP-FR-3857 Final Report for Validation of Determination of (b) (4) Using the (b) (4)
58. VP-FR-3900 Final Report for Comparability Testing of Bivigam Drug Substance for the Transfer of (b) (4) Based Method SOP QC2194 to (b) (4) Method SOP QC3192 (2014)
59. VP-FR-0605 (b) (4) Anti-HBs Potency in Nabi-HB (b) (4) Final Container (effective 24-FEB-04)
60. VP-FR-0605-4 (version 4)
61. Validation Study 11054-ALC-VALIDATION – Measurement of Residual and Total Alcohol by (b) (4)
62. VP-FR-3654 – Final Report for the Validation of (b) (4) Test for the Quantification of Measles Antibodies in Biotest IGIV Drug Product (approved 08-APR-11)
63. VP-FR-3548 Validation of the (b) (4) Method for the Determination of (b) (4) in Biotest Immune Globulins, Intravenous Drug Product (no date)
64. VP-FR-3526 Final Report of Validation of “Determination of (b) (4) in IGIV Product by (b) (4) (no date)
65. VP-FR-0429 Method Validation of the Chloride Assay in Immune Globulin Preparation (effective 27-MAR-00, Nabi)

66. VP-FR-0429-4 Addendum to Method Validation of Chloride Assay Using (b) (4) (no date)
67. VP-FR-3262 Method Validation of (b) (4) of IgG Products (approved 12-FEB-07, Nabi)
68. VP-FR-3262-1 Assay Reagent Stability Evaluation for Determination of Protein Composition and Purity in Human IgG Products using (b) (4)
69. VP-FR-3390 Method Validation of (b) (4) Determination of IgG Products in IGIV formulation (b) (4) (approved 04-JUN-09)
70. VP-FR-0107-3 Method Validation of Glycine Assay by (b) (4) (approved 12-OCT-06, Nabi)
71. VP-FR-0107-4 Addendum to Method Validation of Glycine Assay by (b) (4) (no date)
72. VP-FR-3545 Final Report- Method Validation for the Detection of Human Serum Proteins (Human Identity) in IGIV and Nabi-HB Final Product Samples (approved 08-MAR-10)
73. VP-FR-0099 Method Validation Final Report – Determination of Triton X-100 Concentration in Aqueous Samples Using (b) (4) (effective 23-APR-1998)
74. VP-FR-0099-3 Stability Evaluation of Triton X-100 Standard Solution for Triton X-100 Assay by (b) (4) (no date)
75. VP-FR-0099-4 Addendum to Method Validation of Triton X-100 Assay by (b) (4) (no date)
76. VP-FR-0164 Method Validation Final Report – Determination of TNBP in Aqueous Samples Using (b) (4)
77. VP-FR-0164-2 Stability Evaluation of TNBP Standard Solution for TNBP Assay by (b) (4) (no date)
78. VP-FR-0164-3 Addendum to Method Validation of TNBP Assay by (b) (4) (no date)
79. VP-IR-3854 Validation of Method: Determination of Residual Alcohol in IgG (b) (4) Samples by (b) (4) (no date)
80. VP-IR-3854-2 Interim Report to Validation of Method: Determination of Residual Alcohol in IgG (b) (4) Samples by (b) (4) / Drug Product Matrix Study (no date)
81. L-09-011 Validation Study: Measurement of Residual and Total Alcohol by (b) (4)
82. FR-2014-03 Comparability/Equivalency Study for the Transfer of the Assay for Determination of Residual Alcohol in IgG In-(b) (4) Samples by (b) (4) to Biotest Pharmaceuticals Corporation (no date)
83. VP-FR-3372 Determination of IgA content in IVIG<sup>(b) (4)</sup> by (b) (4) (no date)

**Supporting Documents in BLA Amendment 13 (STN 125590/0.13) that were reviewed:**

1. 1.14.1.3 Draft Labeling Text – contains Proposed Labeling Text (Word, SPL, Word – Track Changes versions).

**Supporting Documents in BLA Amendment 21 (STN 125590/0.21) that were reviewed:**

1. 1.11.1 Quality Information Amendment –Response to FDA Request for Assay Information (January 08, 2016)
2. 3.2.S.4.3 Validation of Analytical Procedures – Endotoxin
3. 3.2.P.5.2 Analytical Procedures – (b) (4)
4. 3.2.P.5.3 Validation of Analytical Procedures – (b) (4)
5. Report 20150624-1 Requalification of the Alert Level Control for IGIV<sup>(b) (4)</sup> Assay (dated 24-JUN-15)
6. 3.2.P.5.6 Justification of Specifications – (b) (4)
7. 3.2.P.6 Reference Standards or Materials

**Supporting Documents in BLA Amendment 22 (STN 125590/0.22) that were reviewed:**

1. 1.11.4 Multiple Module Information Amendment - Response to FDA Request for Changes to the Package Insert and Drug Product Specifications (January 11, 2016)
2. (b) (4) Justification
3. Technical Report – TEC-13-003-RPT: II-04: Evaluation of ADMA Biologics RSV-IGIV preparations for efficacy in the Cotton Rat Model of RSV and determination of serum RSV Neutralization Titers (approved 29-JAN-15)
4. Technical Report – TEC-14-002-RPT: II-89: Normal and Immunosuppressed Cotton Rat: ADMA Anti-RSV Treatment Study and Determination of Serum RSV Neutralization Titers (approved 29-JAN-15)

5. Technical Report – TEC-14-004-RPT: II-82: Immunosuppressed Cotton Rat: ADMA Anti-RSV Prophylaxis Study and Determination of Serum RSV Neutralization Titers (approved 29-JAN-15)
6. Technical Report – TEC-15-008-RPT: Prophylactic Administration of RI-002 (IGIV): Administered by Intraperitoneal Injection for Antiviral Activity in the Palivizumab-resistant (PR) RSV/A/Tracy-infected Cotton Rat Model (approved 22-SEP-15)
7. Technical Report – TEC-16-001-RPT: Report No. 3 AB-16-01: Determination of RSV/A/Tracy-Specific Neutralizing Antibody Titer in Samples of Citrated Human Plasma by a Microneutralization Assay (dated 28-JAN-16, addendum issued 1-FEB-16)
8. Technical Report – TEC-16-002-RPT: Review of RI-001 and RI-002 Relative Potencies (approved 21-JAN-16)
9. Vendor Test Result Report - Test Report #TR-RI-16-005: (b) (4) Lot no. (b) (4) Purity Assay by QC2161, test date: 22-JAN-16 – results and (b) (4) (approved 29-JAN-16)
10. 3.3 Literature References – 28 papers, including: Siber GR. Comparison of Antibody Concentrations and Protective Activity of Respiratory Syncytial Virus Immune Globulin and Conventional Immune Globulin. *J Infect Dis* 1994; 169:1368=73.
11. 5.4.5.4 Legacy Clinical Study Report – Study RI-001 – Clinical Summary Report: A Compassionate Use Study Using a Hyperimmune Intravenous Immunoglobulin Containing Standardized Levels of High Titer Neutralizing Antibodies to Respiratory Syncytial Virus for Rescue of Patients with Lower Respiratory Tract RSV (dated 12-NOV-15)
12. 5.4 Literature References – 43 papers

**Supporting Documents in BLA Amendment 24 (STN 125590/0.24) that were reviewed:**

1. 1.11.1 Quality Information Amendment –Response to FDA Request for Information (January 21, 2016)
2. (b) (4) Protocol – PR-10028-4: Qualification Requalification and Stability Monitoring of CAT Reference Standard (implemented 27-MAY-15)
3. (b) (4) Certificate of Analysis - COA071615: (b) (4) (requalification date: 27-MAY-15, document signed 16-JUL-15) – (b) (4) Reference Reagent (b) (4). Analysis conducted on a (b) (4) instrument.
4. (b) (4) Protocol – PR-10028-5: Qualification Requalification and Stability Monitoring of CAT Reference Standard (implemented 7-DEC-15)
5. (b) (4) Stability Summary: (b) (4) Reference Standard (b) (4) (signed 5-FEB-16)

**Supporting Documents in BLA Amendment 34 (STN 125590/0.34) that were reviewed:**

1. 1.11.1 Quality Information Amendment – Response to FDA Request for Information –Late Cycle Meeting Notes (April 13, 2016) – proposed identity test for RI-002, optimization of the alcohol method,
2. Method SOP LAB3014 Hepatitis B Immune Globulin Identification Procedure for Final Container Using the (b) (4)

**Supporting Documents in BLA Amendment 36 (STN 125590/0.36) that were reviewed:**

1. 1.11.4 Multiple Module Information Amendment – Response to FDA Request for Information – (b) (4) Issues – Late Cycle Meeting Notes (May 9, 2016)
2. Supplemental Information to Support the Inclusion of “Standardized (b) (4) in the Product Specifications and Package Insert for ASCENIV (RI-002) – with examples of package inserts with disclaimer language

**References:**

Siber GR, Leszczynski J, Penn-Cruz V, Ferren-Gardner C, Anderson R, Hemming VG, Walsh EE, Burns J, McIntosh K, Gonin R, Anderson LJ. 1992. Protective activity of a human respiratory syncytial virus immune globulin prepared from donors screened by microneutralization assay. *J Infect Dis* 165:456-63.

VP-FR-3565 Validation of Diphtheria Toxoid IgG EIA Method for the Quantitation of Diphtheria Antitoxin Antibodies in the Biotest-IGIV Drug Product (approved 11-JUN-10)  
CMC Review STN 125590/0 ML Virata-Theimer, L Deng