



Food and Drug Administration  
Center for Biologics Evaluation and Research  
10903 New Hampshire Ave  
Silver Spring MD 20993-0002

**To:** Administrative File:  
STN 125590/0 (DCC Login ID#61938) ASCENIV®, Human Immune Globulin, Intravenous 10% (RI-002)

**From:** CDR Jeremy L. Wally, PhD, CMC/Facilities and Equipment Reviewer, CBER/OCBQ/DMPQ/MRB2

**Through:** John A. Eltermann, Division Director, CBER/OCBQ/DMPQ  
LCDR Qiao Bobo, Branch Chief, CBER/OCBQ/DMPQ/MRB2

**CC:** Pete Amin, Acting Team Leader, CBER/OCBQ/DMPQ/MRB2  
Pei Zhang, Chair, CBER/OBRR/DHRR/LPD  
Yu Do, RPM, CBER/OBRR/PPMS  
Lu Deng, Product Reviewer, CBER/OBRR/DHRR/LPD

**Subject:** Biologics License Application (BLA)

**Indication/  
Drug Info:** Intravenous infusion for the use in the treatment of Primary Immunodeficiency Diseases (PID)

**Applicant:** ADMA Biologics, Inc.

**License Number:** N/A

**Facility Site:** Biotest Pharmaceuticals Corporation in Boca Raton, Florida (FEI: 1000525461); and (b) (4)

**Action Due Date:** July 30, 2016

**Recommendation:** Issuance of a Complete Response Letter (see comments below)

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**Product Summary**

RI-002 is a human immunoglobulin product supplied as a solution for intravenous infusion containing 10% human protein of which at least 96% is Immunoglobulin G (IgG) obtained from pooled plasma from normal source donors (b) (4)

(b) (4). The pooled plasma is concentrated using a modified classical Cohn-Oncley cold-alcohol fractionation process with two added viral reduction steps.

RI-002 has (b) (4) formulation and protein concentration as BIVIGAM (another immune globulin intravenous or IGIV), with the only differences in manufacture being (b) (4) for RI-002. The RI-002 drug substance is manufactured at the Biotest Pharmaceuticals Corporation (Biotest) facility in Boca Raton, Florida (FEI: 1000525461) using the same processes and equipment as used for other IGIV drug substances manufactured at this facility (including BIVIGAM). The RI-002 drug product is sterile filtered, filled, labelled and packaged at the (b) (4) using the same processes and equipment as are used for BIVIGAM (also manufactured at this facility). The RI-002 drug product is provided in 50 mL clear, (b) (4) glass vials with bromobutyl rubber (b) (4) stoppers and aluminum seals with plastic flip-off caps containing at least 50 mL ( $\geq 5$  g) of the RI-002 drug product (the identical container closure as is used for BIVIGAM).

Based upon review of the original submission and amendments of August 31, 2015 (STN 125590/6) and January 22, 2016 (STN 125590/17) for this BLA, a Complete Response letter should be sent to ADMA Biologics, Inc. (ADMA), with the following comments:

- 1. We are unable to complete a final approval action for your biologics license application until inspection issues have been resolved from the January 26 to March 3, 2016, inspection of the Biotest facility in Boca Raton, Florida.*
- 2. We are unable to complete a final approval action for your biologics license application until the outstanding compliance issues from the (b) (4), inspection of the (b) (4), have been resolved.*
- 3. Please provide a summary or study report for the RI-002 drug substance process validation performed at the Biotest facility in Boca Raton, Florida that includes a description of any deviations and corrective actions for the (b) (4) drug substance batches manufactured in support of this BLA.*
- 4. Please provide a summary or study report for the RI-002 drug product process validation performed at the (b) (4) that includes a description of any deviations and corrective actions for the (b) (4) drug product batches manufactured in support of this BLA.*
- 5. Please clarify if the (b) (4) are used to store other IGIV (b) (4) manufactured in the Biotest facility in Boca Raton, Florida.*

6. *Please provide a summary or any study reports for container closure integrity testing of the (b) (4)*
7. *Please provide a summary or any study reports for container closure integrity testing performed on the final container closure system used for the RI-002 drug product.*
8. *Regarding the most recent re-qualification study reports for the (b) (4) autoclaves (31-PQVR-32120-012 for autoclave (b) (4) and 31-PQVR-32121-027 for autoclave (b) (4)) provided in the amendment of January 22, 2016, we noted that the required lethality is based upon a theoretical D-value of (b) (4) for the biological indicators. Please provide the actual D-values for the biological indicators used in these studies and the results of calculations of the Sterility Assurance Level obtained for each load pattern (maximum and minimum loads).*
9. *The study report (33-APVR-517-034) for the most recent media fill for the (b) (4) facility provided in the amendment of January 22, 2016, states that there was an action level excursion for (b) (4) during sterile filtration. Please provide the investigation report for this excursion.*
10. *Please clarify if the shipping of (b) (4) RI-002 drug substance from the Biotest facility in Boca Raton, Florida to the (b) (4) uses the same procedures and container as are used for BIVIGAM. If this is not the case, then please submit the validation of shipping under worst-case conditions (b) (4) as you describe in the amendment of January 22, 2016.*
11. *Please clarify if the shipping of RI-002 drug product from (b) (4) uses the same procedures and container as are used for BIVIGAM. If this is not the case, then please submit the validation of shipping under worst-case conditions (b) (4) as you describe in the amendment of January 22, 2016.*

### **Contents of Submission**

This is an electronic submission in eCTD format. The original submission contains the following documentation that was reviewed: a FDA Form 356h for the above referenced product, a cover letter and a request a categorical exclusion to the environmental assessment in Section 1, summary documents for the drug substance, drug product and manufacturing facilities in Section 2.3, and CMC information on the drug substance, drug product and manufacturing facilities in Section 3. The amendment of August 31, 2015 (STN 125590/6) contains the following documentation that was reviewed: a FDA Form 356h for the above referenced product, a cover letter, and a response to the Information Request of August 26, 2015 in Section 1. The amendment of January 22, 2016 (STN 125590/17) contains the following documentation that was reviewed: a FDA Form 356h for the above referenced product, a cover letter, and a response to the Information Request of August 26, 2015 in Section 1, and CMC information on the drug product in Section 3.2.P.3.3 and on the (b) (4) facility in Section 3.2.A.1.

### **Review**

This BLA was received on July 31, 2015, and on Michael Vardon was assigned as the CMC/Facilities and Equipment Reviewer. Based upon review of the original submission, an Information Requests containing one comment and an Information Requests containing nine comments were emailed to ADMA on August 26, 2015 and January 5, 2016, respectively. ADMA responded to these Information Requests in amendments of August 31, 2015 (STN 125590/6) and January 22, 2016 (STN 125590/17), respectively. The responses to these Information Requests are reviewed below under *Information Requests*. This BLA was subsequently re-assigned on January 15, 2016.

### *Environmental Analysis*

ADMA requests a categorical exclusion to the environmental assessment requirements in accordance with 21 CFR §25.31(c). In addition, to their knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

***Reviewer's Comments:*** *The request for categorical exclusion from environmental assessment from the above product is accepted.*

### *Product Summary*

RI-002 is a human immunoglobulin product supplied as a solution for intravenous infusion, and containing 10% human protein, of which at least 96% is IgG (100 mg IgG/mL) formulated with  $120 \pm 20$  mM sodium chloride,  $245 \pm 45$  mM glycine, and  $0.2 \pm 0.05\%$  polysorbate 80 at a pH of  $4.3 \pm 0.3$ . The RI-002 drug product is a sterile, non-pyrogenic aqueous preparation of immunoglobulins obtained from pooled plasma from normal source donors (b) (4)

. The pooled plasma is concentrated using a modified classical Cohn-Oncley cold-alcohol fractionation process with two added viral reduction steps: solvent/detergent treatment to eliminate enveloped viruses, using Tri-n-butyl phosphate and Triton X-100, and virus filtration using a 35 nm virus filter. The mean consistency of the antibody spectrum in the RI-002 drug product is ensured by using a plasma pool of at least (b) (4) donors for each production batch. The distribution of IgG1, IgG2, IgG3 and IgG4 subclasses is stated to be similar to that of normal plasma. The RI-002 drug product is clear to slightly opalescent and colorless, and is provided in 50 mL clear, (b) (4), borosilicate glass vials with gray, bromobutyl, rubber (b) (4) stoppers and aluminum seals with plastic flip-off caps containing at least 50 mL ( $\geq 5$  g) of the RI-002 drug product. The target volume during fill is (b) (4) mL (determined (b) (4) by emptying individual containers and therefore represent the extractable volume).

### *Drug Substance Manufacturing Facilities*

The following facilities are involved in the manufacture of the RI-002 drug substance:

| Name and Address   | Responsibility | FDA Inspectional History |
|--|----------------|--------------------------|
| ADMA Biologics, Inc.<br>465 Route 17 South<br>Ramsey, New Jersey 07446 | (b) (4)        | N/A                      |

| Name and Address   | Responsibility   | FDA Inspectional History                            |
|--|--|---|
| ADMA BioCenter<br>6290 Jimmy Carter Blvd<br>Norcross, Georgia 30071  | Source plasma provider   | N/A   |
| Biotest Plasma (Corporate Office)<br>5800 Park of Commerce Blvd., N.W.<br>Boca Raton, Florida 33487                      | Source plasma provider, and pre-production lot designated plasma storage | N/A   |
| Biotest Pharmaceuticals Corporation<br>5800 Park of Commerce Blvd., N.W.<br>Boca Raton, Florida 33487<br>FEI: 1000525461 | (b) (4)  | 01/26/2016-03/03/2016*<br>08/05/2014-08/14/2014 OAI |
| (b) (4)  | (b) (4)  | N/A   |
| (b) (4)  | (b) (4)  | N/A   |
| (b) (4)  | (b) (4)  | N/A   |
| (b) (4)  | (b) (4)  | N/A   |

OAI = Official Action Indicated

\*A warning letter was issued for this facility on November 25, 2014, after the 2014 Team Biologics inspection was classified as OAI. A follow-up Team Biologics inspection of this facility was performed in 2016 and an FDA Form 483 was issued at the conclusion of this inspection. A classification decision for this inspection was not made at the time of finalization of this memo and therefore the facility was not considered to be in compliance.

**Reviewer's Comments:** *The Biotest facility in Boca Raton Florida was not in compliance at the time of finalization of this memo due to a pending decision on the Team Biologics inspection of this facility. Therefore a Complete Response letter should be issued for this BLA. See Complete Response letter comment #1.*

**Drug Product Manufacturing Facilities**

The following facilities are involved in the manufacture of the RI-002 drug product:

| Name and Address   | Responsibility  | FDA Inspectional History                  |
|--|---|---|
| ADMA Biologics, Inc.<br>465 Route 17 South<br>Ramsey, New Jersey 07446 | Oversight of manufacture and release of final product.  | N/A                                       |
| (b) (4)  | Sterile filtration, aseptic vial filling, labelling, packaging, and final container release testing | (b) (4) VAI<br>(b) (4) VAI<br>(b) (4) OAI |
| (b) (4)  | Measles potency by neutralization, and polio Types 1, 2 or 3 potency by neutralization              | None**                                    |

| Name and Address | Responsibility   | FDA Inspectional History      |
|------------------|--|-------------------------------|
| (b) (4)          | (b) (4)  | (b) (4) OAI***<br>(b) (4) VAI |
| (b) (4)          | Sterility, and particulate matter testing                        | (b) (4) VAI<br>(b) (4) NAI    |
| (b) (4)          | (b) (4)  | (b) (4) NAI<br>1(b) (4) VAI   |
| (b) (4)          | Pyrogen testing  | (b) (4) VAI<br>(b) (4) NAI    |
| (b) (4)          | Back-up lab for pyrogen testing                                  | (b) (4) NAI<br>(b) (4) NAI    |
| (b) (4)          | Shipment of RI-002 drug product from manufacturer to distributor | N/A                           |
| (b) (4)          | (b) (4)  | (b) (4) NAI                   |
| (b) (4)          | Distribution   | N/A                           |

OAI = Official Action Indicated, VAI = Voluntary Action Indicated, NAI = No Action Indicated

\*\*This drug product release testing facility does not have a compliance history with FDA. See reviewer's comments below.

\*\*\* The most recent inspection of this drug product release testing facility was characterized as OAI and therefore this facility would not be considered to be within compliance. See reviewer's comments below.

**Reviewer's Comments:** *The Biotest facility in Boca Raton Florida was not in compliance at the time of finalization of this memo due to a pending decision on the Team Biologics inspection of this facility. Therefore a Complete Response letter should be issued for this BLA. See Complete Response letter comment #1.*

**Reviewer's Comments:** *It is not clear if any new areas in the (b) (4) facility in (b) (4) will be used to manufacture the RI-002 drug product. ADMA was therefore asked to clarify this point in the Information Request of August 26, 2015 (only comment). ADMA's response is reviewed below under Information Requests.*

**Reviewer's Comments:** *One of the drug product release testing facilities, (b) (4), located at (b) (4)*

(b) (4) [REDACTED], does not have a compliance history with FDA. Due to the change in DMPQ reviewer assignment, this issue was not identified until late in the review cycle and after a recommendation to issue a Complete Response letter due to the compliance issues at the Biotest facility was made. Therefore, a determination regarding whether this facility has a compliance history with a foreign regulatory body to satisfy the requirements to waive inspection of this facility should be made during review of the response to the Complete Response letter.

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**Reviewer's Comments:** One of the drug product release testing facilities, (b) (4) [REDACTED] was not in compliance at the time of finalization of this memo due to the most recent inspection being classified as OAI. Therefore a Complete Response letter should be issued for this BLA. See Complete Response letter comment #2. Due to the change in DMPQ reviewer assignment, this issue was not identified until late in the review cycle and after a recommendation to issue a Complete Response letter due to the compliance issues at the Biotest facility was made.

*Drug Substance Manufacturing Process*

(b) (4) [REDACTED]

(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

*Drug Product Manufacturing Process*

The RI-002 drug product manufacturing process includes final filtration, filling, labeling and packaging. Sterile filtration and aseptic filling of the RI-002 drug product is based on the Biotest IGIV process. Identical vials, stoppers and seals to BIVIGAM (50 mL) are used at the (b) (4) facility for filling. The filtration and filling system is closed, except for steps that occur within a Class (b) (4) environment. The RI-002 drug product manufacturing steps are as follows:

(b) (4)

(b) (4)

**Reviewer's Comments:** *The same processes, equipment (b) (4) and container closure system are used to fill, label, inspect and pack the RI-002 drug product as are used to fill, label, inspect and pack BIVIGAM.*

*Control of Materials*

**Control of Raw Materials Used in Drug Substance Manufacturing**

The starting material for the RI-002 drug substance is source plasma collected from normal, (b) (4) donors at Biotest Pharmaceuticals Corporation (5800 Park of Commerce Blvd., N.W., Boca Raton, Florida 33487; license #1792) and ADMA BioCenter Georgia, Inc. (Suite 210, 6290 Jimmy Carter Blvd., Norcross, Georgia 30071; license #1834), which are stated as being FDA licensed and International Quality Plasma Program (IQPP) certified plasma collection facilities in the U.S. (b) (4)

. Other raw materials are tested

upon receipt (all are visual inspected) and released by Biotest's Quality Assurance department according to written procedures. (b) (4)

**Control of Raw Materials Used in Drug Product Manufacturing**

All excipients are introduced into the product during formulation of the RI-002 (b) (4).

*Control of Intermediates (Storage Conditions)*

**Drug Substance Intermediate Hold Times**

(b) (4)

(b) (4)

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**Drug Product Process Validation**

(b) (4) lots of RI-002 drug product were manufactured as shown in the following table:

(b) (4)

Certificates of Analysis for these RI-002 drug product lots are provided in the original submission. Release testing results for these RI-002 drug product lots are reviewed below under *Batch Analysis*.

**Reviewer's Comments:** ADMA did not provide a summary or study report for the RI-002 drug product process validation nor provide a list of any deviations/corrective actions for the (b) (4) drug product batches manufactured in support of this BLA. This information should be requested in the Complete Response letter. See Complete Response letter comment #4 provided above.

*Other Validations*

(b) (4)

(b) (4)

(b) (4)

**Shipping Validations**

(b) (4)

(b) (4)



(b) (4)



Drug Product Shipping Validations

No validation of shipping of the drug product was provided in the BLA.

*Reviewer's Comments:* ADMA did not provide a validation of shipping of the RI-002 drug product from the (b) (4) . ADMA was therefore asked to a summary of this validation in the Information Request of January 5, 2016 (comment #9). ADMA's response is reviewed below under Information Requests.

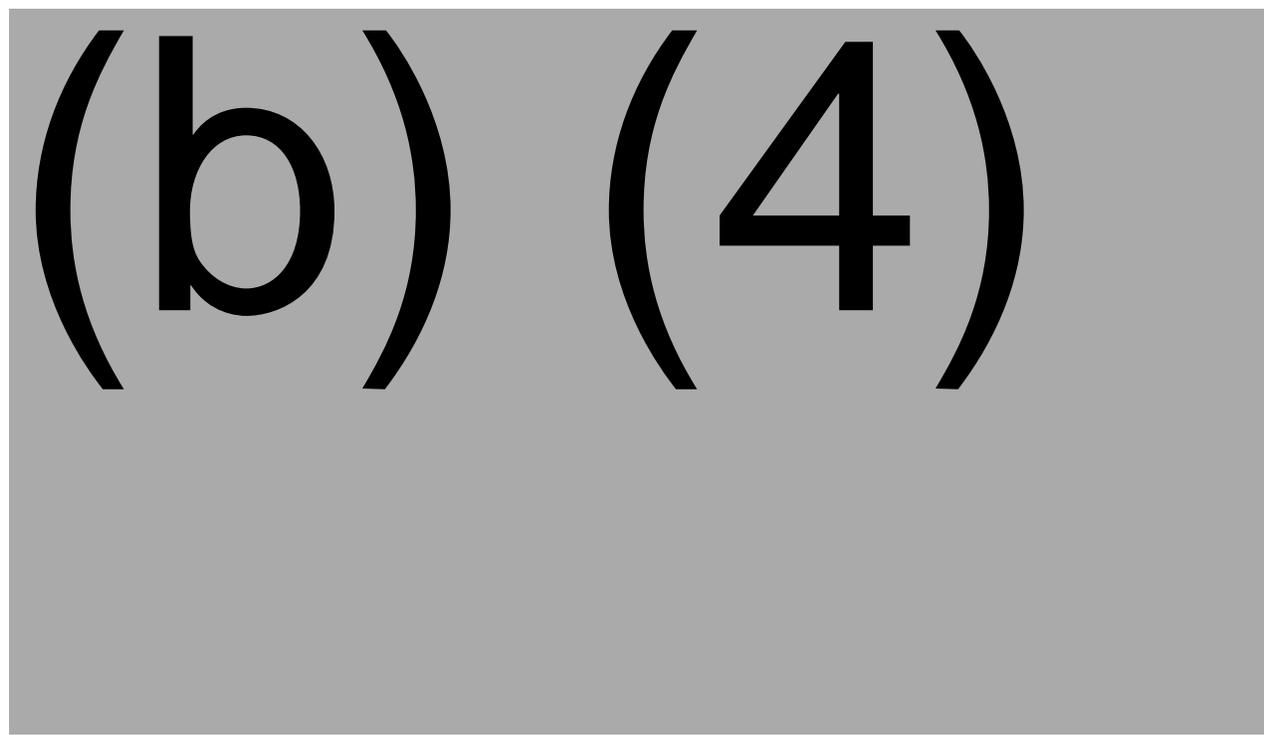
*Specifications*

**Drug Substance Specifications**

(b) (4)



(b) (4)



**Drug Product Specifications**

The release specifications for the RI-002 drug product are shown in the following table:

| Test Parameters     | Specifications   | Method            | SOP                       |
|---------------------|--|-------------------|---------------------------|
| (b) (4)             |  |                   |                           |
| Appearance          | Clear to slightly opalescent; colorless to pale yellow; free of turbidity; free of visible particles   | Visual Inspection | (b) (4): QC2130           |
| Chloride            | 100 - 140 mM   | (b) (4)           | (b) (4) QC2059            |
| (b) (4) Purity      | (b) (4)  | (b) (4)           | (b) (4) QC2161            |
| (b) (4) Purity      | ≥96% Gamma Globulin  | (b) (4)           | (b) (4): QC3099           |
| Glycine             | 200-290 mM   | (b) (4)           | (b) (4): QC2105           |
| Identity (b) (4)    | Positive   | (b) (4)           | (b) (4) QC2049            |
| (b) (4)             | (b) (4)  | (b) (4)           | (b) (4): QC3139           |
| Particulate Matter  | (b) (4)  | (b) (4)           | (b) (4)<br>STP0011        |
| pH                  | 4.0-4.6  | pH                | (b) (4): QC2129           |
| Polysorbate 80      | 0.15-0.25%   | (b) (4)           | (b) (4): QC2255           |
| Potency: Anti-HBs   | (b) (4) ≥CBER reference standard, Lot 176  | (b) (4)           | (b) (4) QC3014            |
| Potency: Diphtheria | (b) (4)  | (b) (4)           | (b) (4)<br>: QC/1143/01   |
| Potency: Measles    | (b) (4) CBER reference standard, Lot 176   | Neutralization    | (b) (4)<br>: V-6087/01-10 |
| Potency: Polio      | Type 1: (b) (4) CBER reference standard, Lot 176 or<br>Type 2: (b) (4) CBER reference standard, Lot 176 or<br>Type 3: (b) (4) CBER reference standard, Lot 176 | Neutralization    | (b) (4)<br>: V5355/04-09  |
| (b) (4)             | (b) (4)  | (b) (4)           | (b) (4)                   |
| (b) (4)             | (b) (4)  | (b) (4)           | (b) (4)                   |
| Protein Content     | 90-110 g/L   | (b) (4)           | (b) (4): QC2100           |

| Test Parameters | Specifications                                       | Method  | SOP                |
|-----------------|--|---------|--------------------|
| Pyrogenicity    | Meets (b) (4) requirements at the 21 CFR 610.13 dose | (b) (4) | (b) (4) 16E-02     |
| Sterility       | Meets 21 CFR 610.12 requirements                     | (b) (4) | (b) (4)<br>STP0077 |

\*Original specification of (b) (4) and alert limit of (b) (4) CBER (b) (4) was based upon method QC2194 which used the (b) (4) and an endpoint assay. The current method uses the (b) (4) assay. A stability evaluation for (b) (4) is required before release.

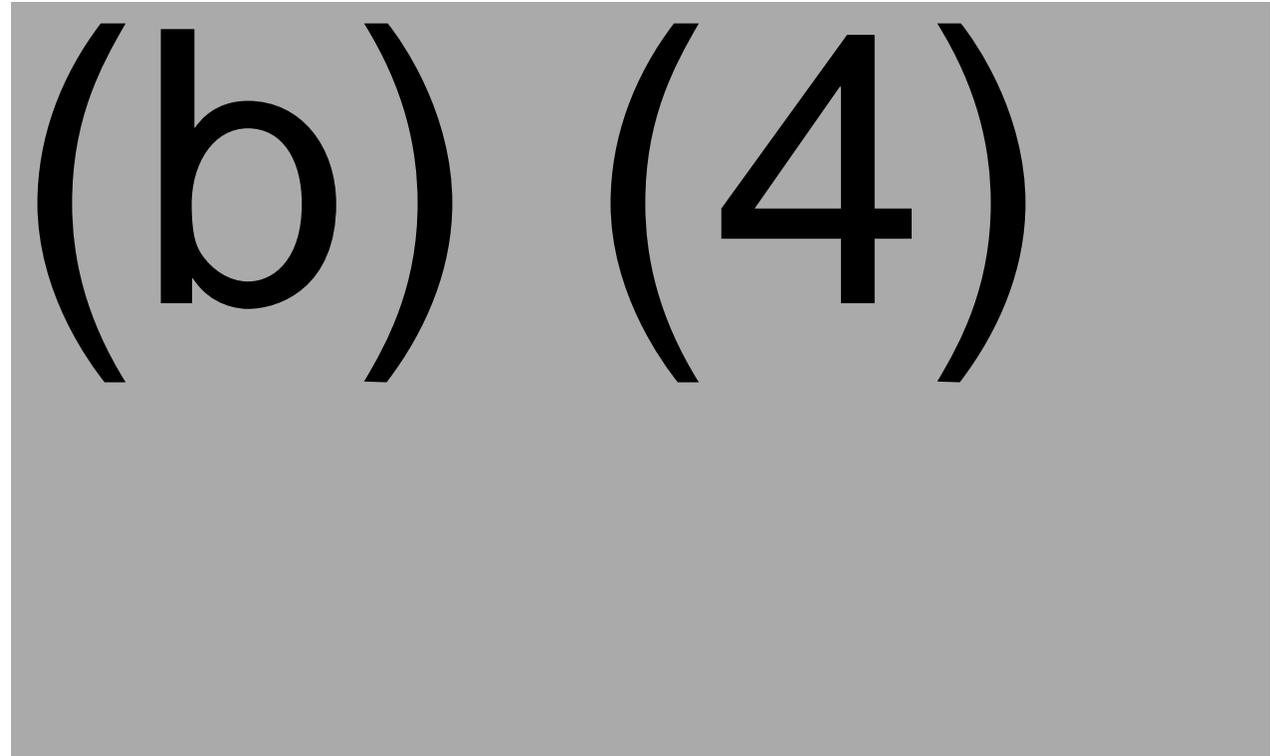
\*\*Lots with initial test results above the specification limit are retested (b) (4) times with independent samples in independent assay runs and investigated as per Biotest's SOP for investigations to determine if any out of trend in process test results or processing conditions occurred during manufacture of the lot. If (b) (4) of 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. Lots with alert limit results are retested (b) (4) times with independent samples in independent assay runs. If (b) (4) of the retest results have a ratio (b) (4) and the average of the original result and the (b) (4) retest results is (b) (4), the lot is released.

*Batch Analyses*

(b) (4)



(b) (4)



(b) (4)

(b) (4)

**Drug Product Batch Analyses**

(b) (4) batches of RI-002 drug product (lots (b) (4) were manufactured using the proposed clinical manufacturing process and released based on the specifications that were current at the time of testing by (b) (4)/ADMA. All batch analysis data were generated by Biotest except where noted. Biotest was responsible for routine testing of the RI-002 drug product except for (b) (4) potency testing, which was conducted by (b) (4)

For future commercial lots, (b) (4) potency testing is to be performed by (b) (4)

|            | Drug Product Lot Number |
|------------|-------------------------|
| (b) (4)    | (b) (4)                 |
| Appearance |                         |
| Chloride   |                         |

|                           | Drug Product Lot Number                                       |
|---------------------------|---|
| (b) (4)<br>Purity         | <div style="font-size: 4em; font-weight: bold;">(b) (4)</div> |
| (b) (4) Purity<br>Glycine |   |
| Identity (b) (4)          |   |
| (b) (4)                   |   |
| Particulate Matter        |   |
| pH                        |   |
| Polysorbate 80            |   |
| Potency: Anti-HBs         |   |
| Potency: Diphtheria       |   |
| Potency: Diphtheria*      |   |
| Potency: Measles          |   |
| Potency: Polio            |   |
| (b) (4)                   |   |
| (b) (4)                   |   |
| Protein Content           |   |
| Pyrogenicity              |   |
| Sterility                 |   |

\*Diphtheria titer testing was removed from release specifications for lots (b) (4) as per ADMA change control CC13-03, IND 15308 amendment serial number 14, dated January 23, 2014. The assay is currently performed for information only as part of the stability testing protocol.

\*\*Thrombogenicity testing was added for lots (b) (4) as per ADMA change control CC13-03, IND 15308 amendment serial number 14, dated January 23, 2014.

**Reviewer's Comments:** *The batches of RI-002 drug product manufactured in support of this BLA met the specification for sterility. Review of the other results is deferred to the assigned product reviewer.*

*Container Closure Systems*

**Drug Substance Container Closure Systems**

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

**Drug Product Container Closure System**

The primary container closure system for the RI-002 drug product consists of the following components:

| Package Component                   | Description   | Manufacturer |
|-------------------------------------|---|--------------|
| 50 mL vial (50.0 mL Fill)           | 20 mm finish; 73.03 ± 0.79 mm (height) x 42.44 ± 0.79 mm (outside diameter); clear (b) (4) borosilicate glass serum bottle; (b) (4) | (b) (4)      |
| Vial Stopper (50 mL vial)           | 20 mm finish serum stopper; bromobutyl rubber formulation (b) (4)   | (b) (4)      |
| Aluminum Flip-Off Seal (50 mL vial) | 20 mm finish; aluminum seal equipped with blue plastic flip-off   | (b) (4)      |

\*Applies only to the commercial RI-002 drug product.

There are differences between the vials and stoppers used for the clinical product and those used for the commercial product (stated by ADMA as being equivalent based upon the specifications). The only differences in the specifications for the commercial product compared to the clinical product are that the 50 mL vials will be pre-sorted at (b) (4) to remove those with visible defects and the flip-off seals will be a matte finish instead of having the words ‘flip-off’ embossed on the seal.

For secondary packaging, each vial is enclosed in a paper unit carton (3.25” x 1.875” x 1.844”) with a tamper evident, adhesive, UV varnish seal (0.812” x 1.187”). The unit cartons are packaged in a ten unit single wall corrugated case (3.75” x 11.6875” x 4.125”).

**Reviewer’s Comments:** ADMA states that the final container closure system used for the RI-002 drug product is the same as the one used for BIVIGAM.

*Container Closure Integrity Testing*

**Drug Substance Container Closure Integrity Testing**

No information on container closure integrity testing for the RI-002 drug substance was provided.

*Reviewer's Comments: ADMA did not provide a summary or any study reports for container closure integrity testing of the (b) (4) used to store the RI-002 drug substance. A summary or any study reports should be requested in the Complete Response letter. See Complete Response letter comment #6 provided above.*

**Drug Product Container Closure Integrity Testing**

ADMA states that container closure integrity testing was performed on the vial, stopper, and seal used for the RI-002 drug product (the same container closure system used for BIVIGAM filled on the same filling machine). ADMA states that the container closure system was found to retain its integrity when challenged with (b) (4) for a specified amount of time using (b) (4).

*Reviewer's Comments: ADMA did not provide a summary or any study reports for container closure integrity testing of the final container closure system used for the RI-002 drug product. Even though this container closure system is already approved for use for BIVIGAM, a summary or any study reports should be requested in the Complete Response letter. See Complete Response letter comment #7 provided above.*

*Stability*

**Drug Substance Stability**

(b) (4)



**Drug Product Stability**

Stability studies were performed according to stability protocol *SP-DF-3052* on (b) (4) conformance lots ((b) (4) stored in the final container at 2-8°C, (b) (4)

(b) (4) Sterility (acceptance criterion meets CFR 610.12 requirements) was scheduled to be tested at months 0, 12, 24, (b) (4) at 5 ± 3°C and at month 3, 6 and 9 at (b) (4)

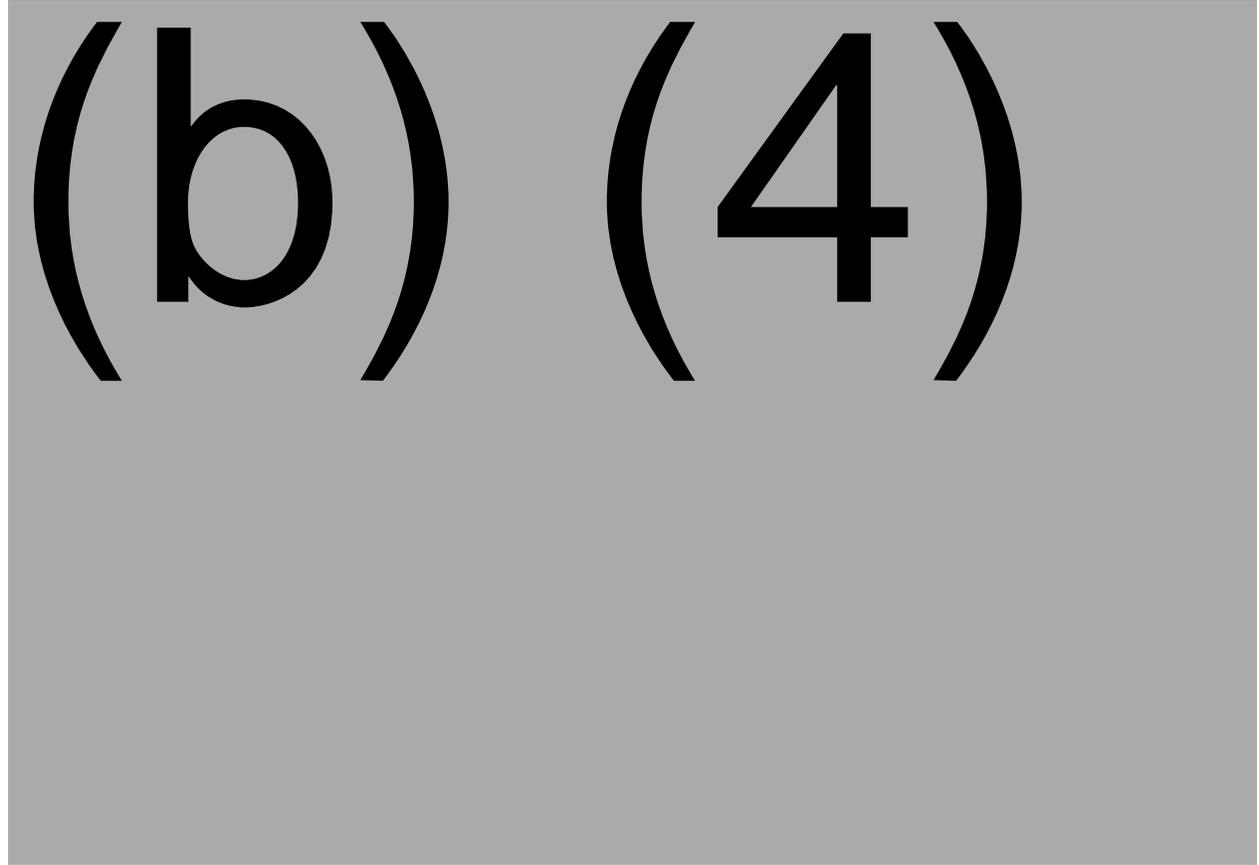
Data out to 12-24 months at 5 ± 3°C, 12 months at (b) (4) is provided in the original submission for the lots. All of the lots met the acceptance criterion for sterility (all results met CFR 610.12 requirements) at all times points tested.

*Facility Information*

**Biotest –Drug Substance Manufacturing**

Facility Description

The manufacturing of the RI-002 drug substance is conducted at the Biotest facility in Boca Raton, FL. Production of RI-002 drug substance is performed in Building <sup>(b)</sup>(4), plasma storage and QC testing of the RI-002 drug substance is performed in Building <sup>(b)</sup>(4), and receipt, sampling and storage of non-refrigerated raw materials is performed in the <sup>(b)</sup>(4). The following rooms in these building are used for the manufacturing of the RI-002 drug substance:



Building <sup>(b)</sup>(4) is a multi-product manufacturing facility that produces IgG bulk drug substances, plasma-derived intermediate pastes and monoclonal antibodies with the manufacturing performed in separate areas for plasma-derived products (referred to as the IgG manufacturing or production area) and monoclonal antibodies (referred to as the mAb manufacturing or production area). All of the plasma-derived products manufactured in the IgG Building <sup>(b)</sup>(4) production are manufactured from source plasma as the starting material. The source plasma is stored and processed for shipping and receiving activities in temperature controlled areas in Building <sup>(b)</sup>(4). Building <sup>(b)</sup>(4) also consists of a multi-testing QC laboratory where analytical testing of IgG bulk drug substances, plasma-derived intermediate pastes and monoclonal antibodies takes place. The following licensed and investigational plasma-derived products are manufactured in the same area as the RI-002 drug substance:

(b) (4)

(b) (4)

- | [Redacted]
- | [Redacted]
- | [Redacted]
- | [Redacted]

(b) (4)

Flow Patterns and Gowning Requirements

***Personnel Flow and Gowning***

The Manufacturing Access Corridor (MAC) is the only access point into the manufacturing area. Gowning and access to various areas within the IgG manufacturing areas is defined in *MAB3096, Gowning for Entrance to the Manufacturing Access Corridor; MFG2022, Gowning for Entrance to the Purification Area; MFG2024, Gowning for Entrance into Room (b) (4)* ;

*MFG2025, Gowning for Entrance to the Fractionation and T/C/P Areas; and MFG2049, Gowning for Entrance to the Purification Wash Room (Room (b) (4) and Autoclave Area (Room (b) (4))* A personnel flow diagram (*BD-PERS-004R10*) is provided in the original submission.

All personnel who work in Class (b) (4) areas and also perform operations in the Class (b) (4) hoods are required to be certified in gowning practices as defined in procedure *QC2088, Gowning Certification for Personnel Working in the Class (b) (4) and Class (b) (4) Areas*. Gowning certification consists of observation and sampling (sleeve, chest, face-mask, hair cover, shoe covers, and hands) with the following acceptance criteria:

- (b) (4) : Finger/Hands (b) (4) Gowning (b) (4)
- (b) (4) : Finger/Hands (b) (4) Gowning (b) (4)

Employees must be re-certified on an (b) (4) basis.

(b) (4)



(b) (4)

[Redacted]

- | [Redacted]
- | [Redacted]
- | [Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

Facility Cleaning

Cleaning requirements for the production areas and corridors are defined in Biotest *SOPs* *MFG2037, Cleaning and Sanitizing of the Purification Area; MFG2038, Cleaning and Sanitizing*

of the Fractionation and (b) (4) Areas; MFG3083, Cleaning of the Manufacturing Hallways, and Storage Areas; and MFG3082, Sanitization of Sprinkler Deluge Drains and Floor Drains in the (b) (4) Areas. In all areas, the cleaning agents are rotated on a (b) (4) basis. The cleaning schedule for the Biotest facility consists of:

- (b) (4)

The following sanitizers are used in the Biotest facility and were previously validated for use as described in study reports FR-2009-10 and FR-2009-10-1: (b) (4)

#### Environmental Monitoring Program

The manufacturing environment in the Biotest facility is monitored routinely (when in operation or not) and on a batch basis (when in operation) for air viables and non-viables as well as for surface viables. The microbial and airborne particulate environmental monitoring (EM) program (and personnel monitoring program) is described in Biotest *SOP QC3151, IgG Facility Routine Environmental Monitoring Program for Controlled Environments*. The number of sampling sites within each room is stated as complying with ISO-14644-1. In the event of an action limit excursion, an incident investigation is performed which includes root cause identification, implementation of any relevant corrective and preventive action, re-sampling, and an evaluation of product impact. ADMA is notified of all excursions and must approve any resultant corrective actions that impact RI-002.

Routine monitoring for air viables and non-viables and surface viables is performed (b) (4) in Grade (b) (4) rooms and (b) (4) in Grade (b) (4) rooms (b) (4) and Fractionation. Routine monitoring for air viables and non-viables and surface viables is performed (b) (4) in Grade (b) (4) areas, (b) (4) in Grade (b) (4) areas and (b) (4) in Grade (b) (4) areas in Purification. Batch monitoring test includes all of the testing described above with the additional use of (b) (4) in Room (b) (4) (measured over a maximum of (b) (4) and the associated laminar airflow hood, and is performed in Rooms (b) (4)

The following environmental limits are set in the Biotest facility:

(b) (4)

(b) (4) used in Room (b) (4) (Grade (b) (4)) and the laminar airflow hood in Room (b) (4) (Grade (b) (4))

Utility Systems

All of the utilities that are used in the production of the RI-002 drug substance have been previously qualified, are routinely monitored, and have preventive maintenance programs. The following qualifications are referenced in the original submission:

(b) (4)

(b) (4)

IQ= Installation Qualification, OQ=Operational Qualification, PQ = Performance Qualification

The relevant utilities are described below.

***Water Systems***

Three types of water are produced at the Biotest facility: (b) (4), and Water For Injection (WFI). The (b) (4) system is used (b) (4)

[Redacted]

***Ethanol System***

The Ethanol System provides ambient ethanol to (b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

**HVAC System**

The HVAC system that supplies air to the IgG manufacturing area is composed of (b) (4) different air-handlers as follows: (b) (4)

(b) (4). The

HVAC system also ensures the required pressure differentials (b) (4) between areas of different classifications and (b) (4) between classified and non-classified areas) to ensure that the air flows from areas of higher classification to lower [except between the (b) (4) and the surrounding staging area (Room (b) (4)). The pressure differentials are monitored on an on-going basis by the Building Monitoring System (BMS) and will alarm if they fall below the set-point. All classified clean-rooms (b) (4)

and their respective air handlers are recertified at least once every (b) (4) which includes (b) (4)

PQ studies were also previously executed under static and dynamic conditions. Air quality was monitored for viable microorganisms and non-viable particulates (see above under *Environmental Monitoring*).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

1 page determined to be not releasable: (b)(4)

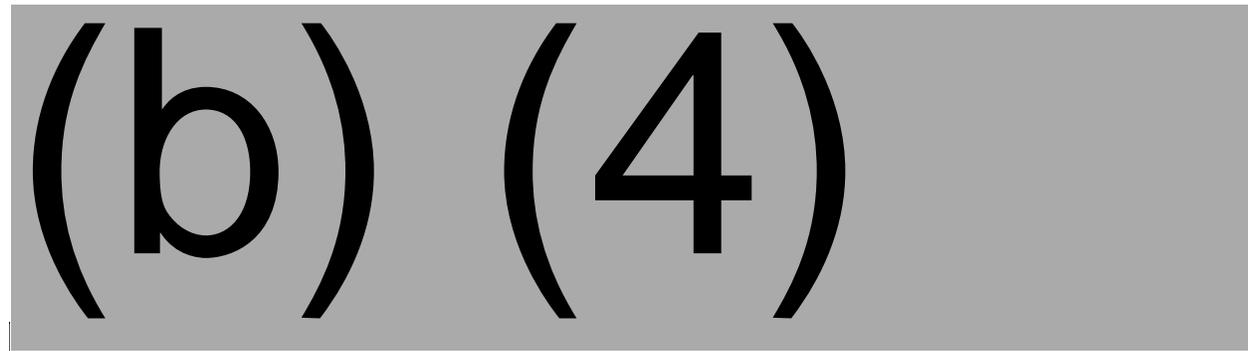
(b) (4)



***Building Management System (BMS-9000)***

The Building Management System (BMS-9000) monitors and records data from critical environmental measurement instrumentation and analyzes the data for alarm processing and operator notification. In addition, the BMS enables archiving and retrieval of data values and alarm records for user requested reports or other system documentation. Changes of state from a normal condition to an alarm condition, and from an alarm condition to a normal condition are recorded in the System Activity Log and transferred to its secure database for long-term archiving and retrieval. Trend values for monitored environments are recorded and uploaded in <sup>(b)</sup><sub>(4)</sub> hour intervals. IQ/OQ was previously completed (reports *VP-FR -3518* and *VP-FR-3518-2*).

(b) (4)



5 pages determined to be not releasable: (b)(4)

**Reviewer's Comments:** ADMA provided the above described cleaning validation reports but did not clarify if they have alert limits for (b) (4) during cleaning verification. ADMA was therefore asked to clarify this point in the Information Request of January 5, 2016 (comment #6). ADMA's response is reviewed below under Information Requests.

Equipment Hold Times

**Dirty Equipment Hold Time (DEHT)**

During cleaning validation, all equipment being cleaned was soiled and then held for a minimum of (b) (4) hours before cleaning and therefore the currently validated DEHT for all equipment is considered to be (b) (4) hours.

**Clean Equipment Hold Time (CEHT)**

Clean hold time studies were incorporated into some of the cleaning validations listed above. If a CEHT is not established, the equipment with the exception of (b) (4) and (b) (4) are cleaned just prior to use (within the same (b) (4) hour period. The CEHT for the (b) (4) are set at (b) (4) days based upon historical data.

(b) (4)

- | [Redacted]
- | [Redacted]
- | [Redacted]

[Redacted]

[Redacted]

[Redacted]

7 pages determined to be not releasable: (b)(4)

(b) (4)

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(b) (4)

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Visual Inspection, Labeling and Chain of Custody

Visual inspection of filled RI-002 drug product is performed according to (b) (4) SOP 0307, *Visual Inspection of Final Dosage*. Final bulk product labels are generated per the appropriate (b) (4) SOP. All labels are inspected and reconciled by QA after packaging and labeling batch activities are finished. All inspected, labeled, and counted filled finished product vials/syringes are placed into inventory pending lot release disposition by QA. Finished product test samples are submitted to Quality Control and all remaining finished product is held in inventory under Quarantine until QA makes a batch disposition decision.

***Reviewer's Comments:** ADMA did not provide enough information on how visual inspection is performed including these defects that are included in the test kit and how any defects are categorized. ADMA was therefore asked to clarify what was provided and to submit information on the most recent re-qualification of these autoclaves in the Information Request of January 5, 2016 (comment #3). ADMA's response is reviewed below under Information Requests.*

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***Reviewer's Comments:** ADMA did not provide enough information on the training and qualification program for visual inspection. ADMA was therefore asked to submit information describing the program in the Information Request of January 5, 2016 (comment #4). ADMA's response is reviewed below under Information Requests.*

### **Information Requests**

#### *Information Request of August 26, 2015*

Based upon review of the original submission, an Information Request containing one comment was emailed to ADMA on August 26, 2015. ADMA responded in an amendment of August 31, 2015 (STN 125590/6). The comment is provided below in bold text, ADMA's response is in normal text and reviewer's comments are italicized.

- 1. Please clarify if any new manufacturing areas that have not been approved by the FDA will be used at Biotest Pharmaceuticals Boca Raton, FL and at (b) (4) sites to produce Immune Globulin Intravenous (Human). If new manufacturing areas are being utilized, please clarify what activities and steps will be performed in each area.**

ADMA states that production for RI-002 will only take place in FDA approved manufacturing areas at both the Biotest facility in Boca Raton, Florida, and the (b) (4)

***Reviewer's Comments:** ADMA has confirmed that no new areas at either facility will be used to manufacture RI-002 drug substance or drug product.*

#### *Information Request of January 5, 2016*

Based upon review of the original submission, a second Information Request containing nine comments was emailed to ADMA on January 5, 2016. Comment #5 was subsequently corrected in an email of January 14, 2016 to change "ppm" to "ppb". ADMA responded in an amendment of January 22, 2016 (STN 125590/17). Each comment is provided below in bold text, ADMA's responses are in normal text and reviewer's comments are italicized.

- 1. Please provide a summary report to better explain what was submitted regarding the most recent (b) (4) depyrogenation oven requalification.**

ADMA provided the most recent requalification study report (31-PQVR-32123-026) for the (b) (4) depyrogenation oven (b) (4) in the amendment. The following information is provided in the study report:

The requalification included (b) (4) (used for RI-002) and consisted (b) (4) There were no deviations.

(b) (4)

(b) (4)

(b) (4)

**Reviewer's Comments:** The re-qualification of the (b) (4) depyrogenation oven (b) (4) is acceptable.

2. Provide a summary report to better explain what was submitted regarding the most recent (b) (4) autoclave requalification for the (b) (4)

ADMA provided the most recent re-qualification study report (31-PQVR-32120-012 for autoclave 6915 and 31-PQVR-32121-027 for autoclave (b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

***Reviewer's Comments:** The acceptance criterion of (b) (4) minutes is based upon a D-value of (b) (4) minute for the theoretical BIs used during the qualification. However, the actual D-value of the BIs was not provided in the study report. Based upon the lowest  $F_0$  obtained of (b) (4) minutes, if the BIs had an actual D-value of (b) (4) minutes and a fractional cycle was not used for the qualification, then a Sterility Assurance Level of (b) (4) or better would not appear to be obtained. Clarification of this point should be requested in the Complete Response letter. See Complete Response letter comment #8 provided above.*

- 3. Provide a complete description of all defects categories found in the visual inspection defect test kit, their overall composition, and number. Include the categories broken down into critical, major, and minor sub-groupings, as appropriate for RI-002.**

(b) (4) states that (b) (4) SOP 0307, *Visual Inspection of Final Dosage Forms*, defines defects as either being Critical Defects (nonconformities that are likely to result in personal injury to the patient and includes any nonconformity that compromises the integrity of the container and risks microbial contamination of the sterile product), Major

A Defects (nonconformities that are potentially hazardous to the patient), Major B Defects (nonconformity leading to serious impairments, such as a malfunction that makes the packaging unusable or reduces efficiency in production, and Minor Defects (nonconformities that do not impair product quality or process capability). The Hands-On Defect Library used for the RI-002 drug product at (b) (4) includes both 50 mL (drug product) and (b) (4) (water in qualification test kit) molded glass vials as shown in the following table:

| Defect Code             | Description                   | Number of Defect (b) (4) Vials (Water) in Qualification Test Kit | Number of 50 mL RI-002 Vials in Hands-On Defect Library |
|-------------------------|-------------------------------|--|---|
| <b>Critical Defects</b> |                               |  |   |
| WRG                     | wrong type container          | 1  | 0   |
| CRK                     | cracked, broken               | 3  | 0   |
| NOS                     | no stopper                    | 2  | 0   |
| NOC                     | no seal                       | 1  | 0   |
| WRS                     | wrong stopper                 | 2  | 0   |
| WRC                     | wrong seal                    | 2  | 0   |
| HIV                     | high volume                   | 2  | 0   |
| LOV                     | low volume                    | 2  | 0   |
| EMP                     | empty container               | 2  | 0   |
| <b>Major A Defects</b>  |                               |  |   |
| B-PTC                   | dark particle                 | 12   | 2   |
| W-PTC                   | light particle                | 4  | 4   |
| B-FIB                   | dark fiber                    | 1  | 1   |
| W-FIB                   | light fiber                   | 3  | 2   |
| <b>Major B Defects</b>  |                               |  |   |
| MGD                     | major glass defect            | 1  | 0   |
| LSC                     | loose seal                    | 2  | 0   |
| DCP                     | discolored or cloudy solution | 2  | 0   |
| <b>Minor Defects</b>    |                               |  |   |
| SDC                     | cosmetic stopper damage       | 2  | 0   |
| DCC                     | discolored seal or cap        | 1  | 0   |
| GRD                     | gross denting of seal         | 5  | 0   |
| ETC                     | etched glass                  | 1  | 0   |
| GLS                     | cosmetic glass defect         | 2  | 0   |

**Reviewer's Comments:** The qualification test kit appears to contain a diverse and comprehensive number of (b) (4) vials while the Hands-On Defect Library only contains vials containing particles or fibers. This appears to be acceptable as it is likely that inspectors who are able to identify the defects in (b) (4) vials would also be able to do so for 50 mL vials.

**4. Provide a complete description of the 100% visual inspect training and qualification program.**

ADMA states that (b) (4) SOP 0311, Training and Qualification of Visual Inspection Operators for Final Dosage Forms details the training and qualification program for visual inspection at (b) (4). Prior to initial training and (b) (4) thereafter, all visual

inspection trainees must pass near vision (b) (4) required) and color perception (must be normal) tests performed by a medically qualified third party. General training includes read and understand training on (b) (4) SOP 0307, (b) (4) and Parenteral Drug Association (PDA) Technical Report No. 43, and continues with use of a Pictorial Inspection Library and the Video Visual Inspection Library. Inspection training is then performed with the Hands-On Defect Library (described in the response to comment #3), and the Standards Library, which contains various types and sizes of particles. When training is complete, the trainee is tested using Qualification/Exam kits with a trainer present to ensure proper technique. The trainee must pass at least (b) (4) test kit exams prior to performing any inspections. Re-testing with the Qualification/Exam kits is then performed (b) (4).

*Reviewer's Comments: The 100% visual inspection training and qualification appears to be adequate.*

**5. Confirm if a more current media fill with the 50 mL vial configuration has been performed. Provide the requalification data if this information is available.**

ADMA provided the study report (33-APVR-517-034) for the most recent media fill for the (b) (4) (using 50 mL vials) in the amendment. The study is reviewed below:

This (b) (4) revalidation was conducted in 2015, and consisted of (b) (4)



*Reviewer's Comments: The media fill appears to have been performed appropriately and to be adequate. However, no explanation/description of the action limit excursion for passive air vials that occurred during sterile filtration was provided. The investigation report should be requested in the Complete Response letter. See Complete Response letter comment #9 provided above.*

6. **Regarding the Biotest equipment cleaning process, it appears the equipment cleaning capabilities can meet WFI (b) (4) specification for (b) (4). Please clarify if Biotest is using alert limits when the final (b) (4) rinse results are higher than (b) (4).**

ADMA states that there are no alert limits for conductivity and (b) (4) of equipment in (b) (4); only action limits. If the final rinse does not meet the requirements for (b) (4) after cleaning, out of specification and deviation reports are required per Biotest SOPs. The action limits at (b) (4)

*Reviewer's Comments: The provide action limits for (b) (4) after cleaning appear to be appropriate.*

7. **Clarify if the (b) (4) filling Suite (b) (4) will be the only filling suite used to manufacture RI-002. The submitted facility diagram indicates (b) (4) filling rooms are located in the same area.**

ADMA states that filtration and filling of the RI-002 drug product is only performed in Filling Suite (b) (4).

*Reviewer's Comments: The response is acceptable.*

8. **Regarding the drug substance shipping validation, please provide a shipping validation summary with data that supports the bulk drug substance transfer from Biotest to (b) (4).**

ADMA states that a bulk RI-002 drug substance shipping study was performed using (b) (4) RI-002 drug substance. (b) (4)

(b) (4) from the Biotest facility in Boca Raton, Florida to the (b) (4) in temperature controlled trucks operated by (b) (4). Shipments were monitored via (b) (4)

(b) (4). There were no temperature excursions.

ADMA states that they use the process qualified in the (b) (4) *Shipping Lane Study* for (b) (4) transfer from the Biotest facility in Boca Raton, Florida to the (b) (4) (b) (4). This study consisted of three runs performed in (b) (4) using (b) (4) shipping units at a temperature set point of 5°C (range 2-8°C) and (b) (4) temperature sensors placed inside the unit (and one outside) shipped from the Biotest

facility in Boca Raton, Florida to the (b) (4). The units remained with the required temperature range throughout shipment.

The current I/O/P/Q Summary Report (*FDX-SOP-ADM-004*) for the (b) (4) (b) (4) Validated Equipment (b) (4) vehicle temperature controlled units) was also provided in the amendment. IQ consisted of temperature control unit verification, (b) (4) datalogger verification and (b) (4). OQ consisted of (b) (4). PQ consisted of (b) (4).

Finally, ADMA also states their intension to perform a PQ on the (b) (4) commercial bulk RI-002 (b) (4) shipment and a (b) (4) RI-002 (b) (4) shipment in (b) (4) to confirm the shipping process maintains the required temperature under extreme conditions.

***Reviewer's Comments:** It is not clear if the shipping of bulk RI-002 drug substance from the Biotest facility in Boca Raton, FL to the (b) (4) uses the same procedures and container as is used for BIVIGAM. If this is the case, then additional shipping validations would not appear to be warranted. If this is not the case, then validation of shipping under worst-case conditions should be requested. Clarification of these issues should be requested in the Complete Response letter. See Complete Response letter comment #10 provided above.*

**9. Provide a summary of the shipping validation that supports the movement of the final drug product manufactured at (b) (4) to the distribution center.**

ADMA states that the same (b) (4) will be used to transport the RI-002 drug product in the final container from the (b) (4) as supported by the I/O/PQ Summary Report (*FDX-SOP-ADM-004*) and the *Shipping Lane Study* supporting shipping between the Biotest facility in Boca Raton, Florida and the (b) (4) (revised under comment #8 above).

ADMA also states their intension to perform a PQ on the first commercial final drug product shipment and final drug product shipments (b) (4) to confirm the shipping process maintains the required temperature under extreme conditions.

***Reviewer's Comments:** It is not clear if the shipping of RI-002 drug product from the (b) (4) uses the same procedures and container as is used for BIVIGAM. If this is the case, then additional shipping validations would not appear to be warranted. If this is not the case, then validation of shipping under worst-case conditions should be requested. Clarification of these issues should be requested in the Complete Response letter. See Complete Response letter comment #11 provided above.*