



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

To: Administrative File:
STN 125590/0.42, ASCENIV, Human Immune Globulin, Intravenous
10% (RI-002)

From: LCDR Silvia Wanis, Pharm.D., CMC/Facilities and Equipment Reviewer,
CBER/OCBQ/DMPQ/MRB2

Through: CDR Qiao Bobo, Branch Chief, CBER/OCBQ/DMPQ/MRB2

CC: Anthony Lorenzo, Team Leader, CBER/OCBQ/DMPQ/MRB2

Subject: Response to Complete Response Letter. Proposed indication is for
Intravenous infusion for the use in the treatment of Primary
Immunodeficiency Diseases (PIDD)

Applicant: ADMA Biologics, Inc.

Facility Site: ADMA Biologics, Inc. in Boca Raton, Florida (FEI: 1000525461); and
(b) (4)

Action Due Date: April 2, 2019

Recommendation: Approval, pending review of the alternate filling site at (b) (4)

SUMMARY

On July 29, 2016, CBER, Office of Blood Research and Review issued a Complete Response (CR) Letter to ADMA Biologics, Inc. in response to their July 31, 2015 BLA original submission. The CR letter included 20 deficiencies, 11 of which are under DMPQ's purview and are discussed in this memo:

- 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 drug substances 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) used to store the RI-002 drug substance.*
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) viables during sterile filtration. Please provide the investigation report for this excursion.*
10. *Please clarify if the shipping of bulk 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) in 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.

On October 1, 2018, CBER received an amendment to BLA STN 125590/0.42 in response to the CR letter for Immune Globulin Intravenous (Human). In this resubmission, ADMA Biologics provided responses addressing the deficiencies in the CR letter. In their cover letter, ADMA Biologics stated they closed the transaction to purchase certain assets to Biotest Pharmaceuticals Corporation (CPC) on June 6, 2017, acquiring the purchase of CPC and provided this change in regulatory contact information for this BLA as follows:

James Maloney
Senior Director, Regulatory Affairs
ADMA Biologics
5800 Park of Commerce NW
Boca Raton, FL 33487
FEI: 1000525461
Tel: 561-989-5745

Responses to deficiencies:

1. ***We are unable to complete a final approval action for your BLA until Inspection issues have been resolved from the January 26 to March 3, 2016, Inspection of the Biotest facility in Boca Raton, Florida.***

ADMA Biologics assumed control and ownership of the Biotest facility in Boca Raton, Florida on June 6th, 2017. The Boca Raton, Florida facility was inspected by FDA on April 3-12th, 2018. ADMA has been informed that the April 2018 inspection has been closed out in a letter dated July 24, 2018 and subsequently the compliance status for the Boca Raton Facility has improved to Voluntary Action Indicated (VAI). It is ADMA's understanding from correspondence with FDA that substantive reviews and approvals may proceed based upon the facilities current VAI status. This would allow for the review of the RI-002 BLA #125590 and such review would not be impacted adversely by the compliance status.

Reviewer's Comment: Response is adequate.

2. ***We are unable to complete a final approval action for your BLA until the outstanding inspection issues from the January 12 to 23, 2015, inspection of the (b) (4) have been resolved.***

ADMA was notified by its contract testing lab, (b) (4) that the warning letter received from the FDA in (b) (4) does not carry over into the laboratory which conducts diphtheria potency testing for ADMA Biologics. ADMA provided a notification letter from (b) (4), dated April 4, 2018, stating such. Additionally, ADMA identified a potential alternate lab for the concentration of diphtheria antitoxin antibodies

in the RI-002 drug product using an antibody (b) (4) method based on (b) (4) for diphtheria antitoxin. (b) (4), completed a feasibility study which confirmed the compendial assay currently performed at their facility is suitable for RI-002. A formal compendial assay verification protocol has been approved and testing has been initiated. Review is deferred to DBSQC.

Reviewer's Comment: The compliance of (b) (4) will be determined in the compliance check. The site information for the alternate site, (b) (4) is incomplete. Requested in IR the information for (b) (4) to be submitted in the 356h, in order to establish compliance status.

In a response dated March 1, 2019, ADMA provided their feasibility study data results with a table showing comparable results for (b) (4). ADMA also initiated a compendial method verification (ADMA-BIO-18-002) on 11/19/2018, but was placed on hold for requalification of a new diphtheria toxin which is projected to be completed on 03/01/2019. The study is projected to restart on 03/04/2019 and is expected to be completed by 03/08/2019 with final report approved by 03/29/2019. ADMA stated that upon completion of the method verification and vendor approval, ADMA will submit data, update the BLA sections and form FDA 356h for review and approval.

Reviewer's Comment: The suitability of (b) (4) is pending compliance check of those facilities. Additionally, the qualification of (b) (4) as an alternate testing laboratory is pending receipt of qualification data for DBSQC review and the submission of the updated 356h for the facility information.

- Please provide a summary or study report for the RI-002 drug substance process validation performed at a 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.***

RI-002 has been developed and owned by ADMA since its inception. The investigational product was produced under contract by (b) (4) and subsequently, Biotest Pharmaceuticals until June 2017. The actual production of RI-002 drug substance utilized the same facilities, equipment and components as was used for BIVIGAM. The RI-002 process included in the BLA utilized (b) (4) production process as BIVIGAM, however, there is one exception:

- RI-002 plasma pool specifications call for the use of source plasma collected from US plasma donors (b) (4) BIVIGAM's production calls for using only (b) (4) source plasma.

In June of 2017, in order to have complete, production, regulatory and quality oversight for RI-002, ADMA acquired the Biotest Therapy Business Unit consisting of the Boca Raton, FL manufacturing facility which also included ownership of the BIVIGAM

product. This acquisition allowed ADMA to access FDA's direct communications to Biotest regarding BIVIGAM reviews and inspections. Only after ADMA acquired the Boca Raton site and the BIVIGAM product, did it become aware of the multiple production and stability issues associated with the BIVIGAM manufacturing process. Given the similarity of BIVIGAM and RI-002's processes, it was concluded that there was likely a common set of operational issues for both products that could lead to undesired outcomes such as (b) (4) failures related to visible (b) (4) particles. Therefore, to achieve effective remediation of common root causes of these events for each product, ADMA recognized that the previously independent investigations and process optimization strategies for BIVIGAM and for RI-002 needed to be combined to address both products simultaneously. ADMA pursued a (b) (4) BIVIGAM and RI-002 process optimization strategy to ensure that both of these products (b) (4) led to a robust and reproducible process that yields high quality product meeting all specified quality and compliance attributes. The process optimization project initiated by ADMA began with a series of pilot-scale studies performed in 2017. The results of these studies formed updated process parameters and controls which were then verified at full production scale in (b) (4) successful BIVIGAM and (b) (4) RI-002 process validation campaigns. The three BIVIGAM lots and three RI-002 lots have all been placed on stability and data for RI-002 is included below. Items pertaining to DMPQ's purview will be discussed below while items pertaining to the Product Office's purview will be deferred to them for review.

In summary, for the three Drug Substance lots for RI-002 Drug Substance, (b) (4) on (b) (4) data is reviewed herein as they pertain to DMPQ's purview. The acceptance criteria for (b) (4). ADMA explained that lots (b) (4) are the historic (clinical) comparison lots to the conformance lots discussed below. ADMA reported all three lots met acceptance criteria at all storage conditions (b) (4).

The three conformance lots of RI-002 Drug Substance; (b) (4) produced with the optimized ADMA-IGIV manufacturing process at (b) (4) according to stability protocol SP-BK-3092, all were reported by ADMA as meeting the acceptance criteria.

ADMA further stated that the three conformance lots of RI-002 drug substance produced using the optimized ADMA IGIV manufacturing process exhibited similar stability profiles and follow in trend with previously produced RI-002 lots at all storage temperatures and conditions. Therefore, RI-002 drug substance stability profiles generated to date support storage of RI-002 Formulated Bulk through (b) (4) conditions will continue through the (b) (4) time point.

Reviewer's Comment: The (b) (4) results are acceptable for the drug substance (DS) process validation. Review of the other DS process validation acceptance criteria is deferred to the product office.

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 deviation and corrective actions for the (b) (4) drug product batches manufactured in support of this BLA.**

ADMA referenced validation report 33-APVR-517-034 and Summary Report of RI-002 clinical lots for the requested information. The (b) (4) RI-002 drug product batches referenced in the original BLA were filled on (b) (4). The (b) (4) equipment has since been decommissioned and is being replaced with a new filling machine with a similar product handling design. ADMA noted that when the next RI-002 fill takes place at (b) (4), the filling process for RI-002 drug substance will be subject to validation and a CBE-30 filing (or other filing classification based upon information we will evaluate in the future) to the Agency. The three most recent batches of RI-002 were not filled at (b) (4) due to the timing and scheduling of their decommissioning/recommissioning of equipment. These three conformance lots of RI-002 were filled at an alternate fill site, (b) (4), and the validation of filling at this site is discussed in section 3.2.P.3.5.

The submission provided the Process Validation at (b) (4) of all the critical utilities (Section 3.2.A.1.4); Critical process equipment, (b) (4) (Section 3.2.A.1.5), validation of Aseptic processing - qualified through process simulation (Media fill) program (Section 3.2.A.1.6), validation of aseptic processing was performed by simulating product fills with the use of growth media according to (b) (4) protocol QUA.PRO.401, Process Simulation of the Aseptic Processing Line. Media fills were performed to validate the aseptic filling process with fill parameters to simulate production conditions.

Process Performance Qualification, ADM.PRD.PRO.023, specified an approach examining three consecutive batches (b) (4) filled at (b) (4) that were required to meet the release criteria. This was done in the period from (b) (4) was used to fill BIVIGAM in vials, which were stoppered and capped. The production record documentation for the three lots filled at (b) (4) confirmed that the BIVIGAM manufacturing, filling, stoppering and capping processes were performed successfully, in which all three lots met the acceptance criteria as defined in ADM.PRD.PRO.023.

Reviewer's Comment: The filling facility at (b) (4) will be reviewed separately from this memo. I will defer to that memo for the evaluation of the new filling line and the results of the PPQ.

5. **Please clarify if the (b) (4) are used to store other IGIV drug substances manufactured at the Biotest facility in Boca Raton, Florida.**

The (b) (4) are used to store other IGIV drug substances, however (b) (4). The (b) (4) containers used for the storage of (b) (4), which include the following: (b) (4)

Reviewer's Comment: Response adequate.

6. **Please provide a summary or any study reports for container closure integrity testing of the (b) (4) used to store in the RI-002 drug substance.**

The (b) (4) is a (b) (4), standard (b) (4) open on one end that is used for (b) (4). Each (b) (4) is visually inspected prior to use for damage at the side walls and seams. Due to the open nature of the (b) (4) integrity testing is not able to be performed.

Regarding the (b) (4), the following studies were conducted to establish an integrity test:

1. The test equipment, (b) (4), was qualified per VP-IOQ-4134/VP-FR-4134 (15 Sep 2016).
2. A development study in which the (b) (4) integrity limit (b) (4) was determined by performing (b) (4) times per VP-DQ-4156. Test method follows ASTM F2095-07 - Standard Test Methods for (b) (4). The (b) (4) integrity limit was documented in VP-FR-4156 (29 Nov 2016).
3. Qualification of Integrity testing of (b) (4) was performed per VP-PQ-4159 and results reported in VP-FR-4159 (13 Dec 2016). The qualification testing consisted of (b) (4) and meets the integrity limit identified in VP-FR-4156.

(b) (4) performs qualification and lot release tests on the (b) (4) as part of its internal processes. The qualification tests include (b) (4) integrity and component/assemblies integrity. The lot release tests include 100% visual testing of (b) (4) and seal, technical drawing compliance, dimensional check, and packaging inspection. In addition, ADMA visually inspects each (b) (4) prior to use.

Reviewer's Comment: Response adequate.

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.***

CTM Manufactured at (b) (4).

As referenced in 3.2.P.2.4, the Container Closure Integrity Testing (CCIT) report for RI-002 drug product (8-SR-220) assures the integrity of the container closure system. The component Receiving Specification Numbers listed in 8-SR-220 are identical to those used for RI-002 clinical product, with the exception of the seal cap color. Likewise, the component Receiving Specification Numbers intended for commercial production are the same components as those used in the clinical product however the specification numbers are ADMA client-specific.

The study reported in 8-SR-220 required at least ^{(b) (4)} vials filled with (b) (4) per run. The acceptance criteria for the study included:

- (b) (4)

(b) (4)

These data support the conclusion that the container closure configuration used for RI-002 CTM was integral and did not allow for (b) (4). Further supporting this are the stability studies performed on all ^{(b) (4)} CTM lots which did not have any sterility testing failures over the course of the study at 2-8°C or (b) (4).

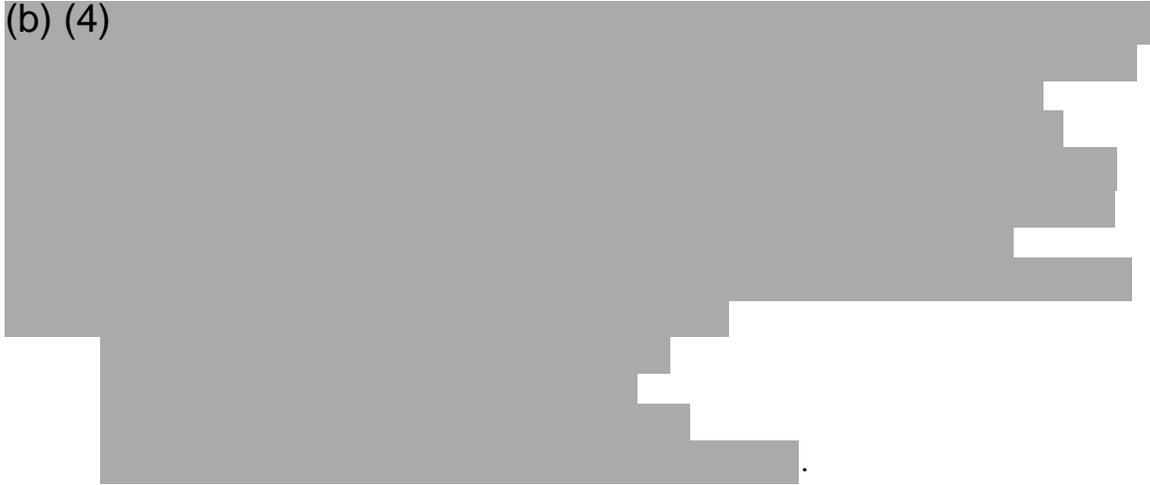
(b) (4)

Table 1, Packaging Components for RI-002 Drug Product 50 mL dose (50 mL vial)

| Package Component | Description | Manufacturer |
|------------------------|---|---|
| Glass Vial | | |
| 50 mL vial | 20 mm finish 73.03 +/- 0.79 mm (height) x 42.44 +/- 0.79 mm (outside diameter) clear (b) (4) borosilicate glass molded serum vial Pre-inspected at (b) (4) . | (b) (4) |
| Stopper | | |
| Vial Stopper | (b) (4): 20 mm finish serum (b) (4) stopper, chlorobutyl rubber formulation (b) (4) | (b) (4) |
| | (b) (4): 20 mm finish serum additive stopper, chlorobutyl rubber formulation (b) (4) | Manufacturing: (b) (4) Processing: (b) (4) |
| Seal | | |
| Aluminum Flip-Off Seal | 20 mm finish Aluminum seal equipped with plastic (b) (4) blue matte top | (b) (4) |

The container closure integrity testing of the container with the new stopper is reported in (b) (4) study number 1089609-S01, and required at least (b) (4) vials distributed from the entirety of the run for (b) (4) testing. The test is performed (b) (4)

(b) (4)



All test units representing the RI-002 primary packaging configuration were shown to be integral by meeting the acceptance criteria above.

(b) (4)



(b) (4)



All test units representing the RI-002 primary packaging configuration were shown to be integral by meeting the acceptance criteria above. Through a combination of (b) (4) testing and the (b) (4) testing, the container closure integrity of the RI-002 units filled at (b) (4) was shown to be robust and that it meets (b) (4) requirements. In addition, the configuration has been shown to be equivalent to the previous configurations via CCIT testing done for the RI-002 units filled at (b) (4)

Reviewer's Comment: Response adequate.

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 calculation of the Sterility Assurance Level obtained for each load pattern (maximum and minimum loads).

ADMA referenced a memorandum dated August 10, 2016 from (b) (4) which provides the sterility assurance levels for (b) (4) sterilization. As noted in the memo, the (b) (4) sterilization methods employed for all porous/hard goods materials and components used at (b) (4) have been validated to provide a Sterility Assurance Level (SAL) of (b) (4). This was confirmed by complete biological inactivation of biological indicators with populations in excess of (b) (4) with (b) (4) values between (b) (4).

Reviewer's Comment: Referenced Memorandum not attached. Requested in Information Request (IR).

In a response dated March 1, 2019, ADMA provided the memorandum dated August 10, 2016. The BIs in requalification report, 31-PQVR-32120-012, had a (b) (4) value of (b) (4) minutes and a population of (b) (4). The minimum and maximum lethality obtained from all maximum load configurations were (b) (4), respectively. The minimum and maximum lethality obtained from all minimum load configurations were (b) (4), respectively. Using these calculations, the probability of a Non-Sterile Unit (PNSU) for all maximum load configurations were between (b) (4). The PNSU for the minimum load configurations were between (b) (4).

The BI's in requalification report, 31-PQVR-32121-027, had a (b) (4) value of (b) (4) and a population of (b) (4). The minimum and maximum lethality obtained from all maximum load configurations were (b) (4), respectively. The minimum and maximum lethality obtained from all minimum load configurations were (b) (4), respectively. Using these calculations, the PNSU for all maximum load configurations were between (b) (4). The PNSU for the minimum load configurations were between (b) (4).

Reviewer's Comment: Response adequate.

9. ***The study report (33-APVR-517-034) for the most recent media fill for the (b) (4) 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.***

During review of 33-APVR-517-034 it was determined that an action level excursion of (b) (4) in the sterile filtration area (room (b) (4)) was incorrectly reported. A comprehensive review of the environmental data was performed and no excursions were noted in the ISO (b) (4) and ISO (b) (4) areas. Positive (b) (4) results were obtained in the formulation area (rooms (b) (4) and (b) (4)), ISO (b) (4) (b) (4) -operation for the media filtration, however they were below the alert limit of (b) (4). A memo detailing the deviation report and CAPA for the validation report error have been provided by (b) (4).

Reviewer's Comment: Response adequate.

10. ***Please clarify if the shipping of bulk 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 worse-case conditions (b) (4) as you described in the amendment of January 22, 2016.***

(b) (4), the shipping of bulk RI-002 Drug Substance from the ADMA Facility in Boca Raton, Florida to the (b) (4) uses (b) (4) procedures and container as are used for BIVIGAM.

Reviewer's Comment: Response adequate.

11. ***Please clarify if the shipping of bulk RI-002 drug product from the (b) (4) 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 worse-case conditions (b) (4) as you describe in the amendment of January 22, 2016.***

(b) (4) will be the distribution center for RI-002 Drug Product, (b) (4) will not be used. The shipping of RI-002 Drug Product from the (b) (4)

uses (b) (4) procedures and container as are used for BIVIGAM.

Reviewer's Comment: Response adequate.