



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

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

From: Yonggang Wang, Ph.D., CMC reviewer, OBRR/DHRR/LPD

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Applicant: ADMA Biologics, Inc.

Product: RI-002, Immune Globulin Intravenous (Human) (Resynrus®).

Subject: Final Review: original BLA, assigned CMC topics – Raw materials and Product Stability sections

RECOMMENDATION

This original BLA submission is recommended for a Complete Response (CR) Letter with the following CR item:

1. The current stability data are inadequate to support the proposed shelf life of 24 months due to out of specification (OOS) test results for Visual Appearance at 9 month (Package lot (b) (4)). Please provide an investigation report which definitely identifies the root cause with the formation of (b) (4) particulates in the final product containers. Please include documentation of what corrective and preventive actions have been implemented in order to preclude a reoccurrence of this issue.

EXECUTIVE SUMMARY

Plasma collection and other materials (Chemicals and Resins) in manufactures were well documented and controlled.

Three types of materials were tested for their stabilities in the stability studies, i.e., (b) (4) [redacted] Final Container Product (Drug Product). The proposed storage conditions for (b) (4) [redacted] were found to be acceptable. The final product is found to be unstable due to the OOS result appeared at 9 month for one package lot (b) (4). The justification provided by sponsor doesn't appear to be acceptable and a Complete Response Letter is recommended to identify the root cause and prevent the reoccurrence of this event.

The proposed dating period of each material was evaluated based on the data from (b) (4) clinical/conformance lots and summarized as follows:

Materials	Proposed by Sponsor	Recommended by Agency
(b) (4)	(b) (4)	Acceptable
(b) (4)	(b) (4)	Acceptable
Drug Product (Final Container)	5 ± 3°C for up to 24 months	<i>Not supported and recommended to identify root cause (CR item 1)</i>

BACKGROUND INFORMATION

RI-002 is a 10% human normal IgG for intravenous administration (IGIV) in a liquid preparation, indicated for the treatment of primary humoral immunodeficiency in adults.

During manufacturing of RI-002, (b) (4), were produced.

RI-002 contains 90-110 g/L protein, of which ≥ 96% is Human Immunoglobulin. It is formulated in the same way as for BIVIGAM, i.e., it has 100-140 mM sodium chloride, 200-290 mM glycine, 0.15-0.25% polysorbate 80, pH 4.0-4.6, and without preservatives.

CMC REVIEW SUMMARY

This review encompasses the raw materials and stability sections from the original BLA submission.

- The submission was received on July 31, 2015.
- Stability updates were requested and received on Jan 11, 2016 (125590/0.16).
- Additional information were requested and received on Feb 24 and 26, 2016 (125590/0.26 & 0.27)

1. Raw Materials – 3.2.S.2.3

- Plasma collection: The starting material is Source Plasma collected under GMP guidelines from two plasma collection facilities in the U.S. Biotest Pharmaceuticals Corporation (license No. 1834), Boca Raton, FL and ADMA BIoCenter Georgia Inc (license No. 1792), (b) (4).
 - The SOPs on donor qualification, plasma collection, processing, testing, rejection, release, storage and shipping are provided.
 - Lookbacks, inventory hold, and traceable procedures are defined.
 - Donors with sufficient RSV titers are selected for the RSV donor program.
- Other materials: All materials, except Triton X-100, TnBP, (b) (4), conforms to (b) (4) monograph. No animal derived materials are used. Materials are tested and released by Quality Assurance department prior to manufacturing.

2. Stability Study Concept and Methods:

The purpose of this study is to provide guidance for assessing the proposed storage conditions and establishing the shelf life for the storable intermediates and final product, without sacrificing the specified product's potency, purity and quality.

(b) (4)

b) (b) (4)

(b) (4)

- c) Drug Product (Final Container Product) – Final product is filled into 50 mL (b) (4) Borosilicate Serum Vial with 20 mm finish serum stopper bromobutyl rubber formulation (b) (4), and the proposed shelf life is up to 24 months when stored at 5 ± 3 °C. (b) (4) lots were placed at the following conditions:
- 5 ± 3 °C for (b) (4) months (sampled at 0, 3, 6, 9, 12, 18, 24, (b) (4) months)
 - (b) (4)

The following test parameters are included: (b) (4)
(b) (4), Appearance (Clear to opalescent, colorless to pale yellow, free of turbidity),
Bioburden (b) (4) purity (b) (4)
(b) (4), Endotoxin (b) (4) pH (4.0-4.6), Anti-HBS (b) (4)
(b) (4) Protein (90-110 g/L), Diphtheria antibody
by (b) (4) Diphtheria antibody by (b) (4) Glycine (200-290
mM), Measles antibody (b) (4) CBER 176 or 177), Polio antibody (type 1 (b) (4)
CBER 176), type 2 (b) (4) CBER 176), type 3 (b) (4) CBER 176), PS 80 (0.15-0.25
%), (b) (4), sterility (meets CFR 610.12 requirements).

Drug Products Lots Placed on Stability

Fill Lot	Package Lot	Date of time 0	Stress (b) (4) Cycles Completed	(b) (4)	Target 5 ± 3°C Time Point Completed
(b) (4)					24 months
					24 months
					24 months
					24 months
					18 months
					18 months

3. RESULTS

- a) (b) (4)
- (b) (4)
- (b) (4)

(b) (4)

(b) (4)

c) Final product:

The stability data from the long-term $5 \pm 3^{\circ}\text{C}$ condition were assigned to one of three stability models, based on the nature of each tested quantitative parameter:

- Separate Intercept, Separate Slope (SISS) where both intercepts and slopes are statistically different among lots
- Separate Intercept, Common Slope (SICS) where lot intercepts are statistically different among lots but lots have a common slope
- Common Intercept, Common Slope (CICS) where neither the intercepts nor the slopes are statistically different among lots

For qualitative parameters, no statistical analysis was performed.

1) Appearance

- Real-time stability: All lots tested passed the acceptance criterion except lot (b) (4), which has an OOS results starting from 9 months in (b) (4) of (b) (4) inspected lots (76%).
- Stress condition: all results met at (b) (4) studies.

- i. No root cause was identified for this OOS result.
- ii. Sponsor compared this lot with a BIVIGAM's lot (b) (4) which has a visual appearance OOS at 12 month in (b) (4) out of (b) (4) vials (94%). Both lots were classified as (b) (4), and the BIGIGAM lot's particulates were larger and more abundant.

2) (b) (4)

3) Anti-HBS

- Real-time stability: SICS model was applied. Decrease trending was predicted. No OOS was expected within 24 months (95% confidence interval).
- Stress condition: The 9 months result for lot (b) (4) failed specifications at (b) (4) the result met specification for (b) (4) studies.

4) (b) (4)

5) Anti-Polio Type 1

- Real-time stability: CICS model was applied. Decrease trending was predicted. No OOS was expected within 24 months (95% confidence interval).
- Stress condition: all results met at (b) (4) studies.

6) Anti-Diphtheria

- All results from real-time, and stress conditions met with specifications. No trending was predicted since all results are well beyond pre-defined specifications.

7) Anti-Measles antibody

- Real-time stability: SISS model was applied. Decrease trending was predicted for all lot except for (b) (4). The trending analysis indicated that the measles antibody may fail specification within 24 months. Updated data will be requested for evaluation.
- Stress condition: all results met at (b) (4) studies.

8) PS80

- Real-time stability: SISS model was applied. Analysis of individual lot showed slopes not significant difference from zero.
- Stress condition: all results met at (b) (4) studies.

9) Total Protein

- Real-time stability: CSCI model was applied. Decreased trend was predicted and OOS is predicted with 24 months.
- Stress condition: all results met at (b) (4) studies.

10) (b) (4) Purity

- Real-time stability: all results met with specifications. The results for (b) (4) were 100%, and (b) (4) were zero.
- Stress condition: (b) (4) failed specifications at 6 months for lots (b) (4).

11) pH and Glycine

- Real-time stability: No trending was predicated since all results are well within specifications.

12) (b) (4)

All results met with specifications. No trending was observed.

13) Color, clarity, turbidity, particles.

- Real-time stability: All results met with specifications except Particles. (b) (4) particles were observed at 9 months for filling lot (b) (4) /package lot (b) (4).
- Stress condition: All results met with specifications.

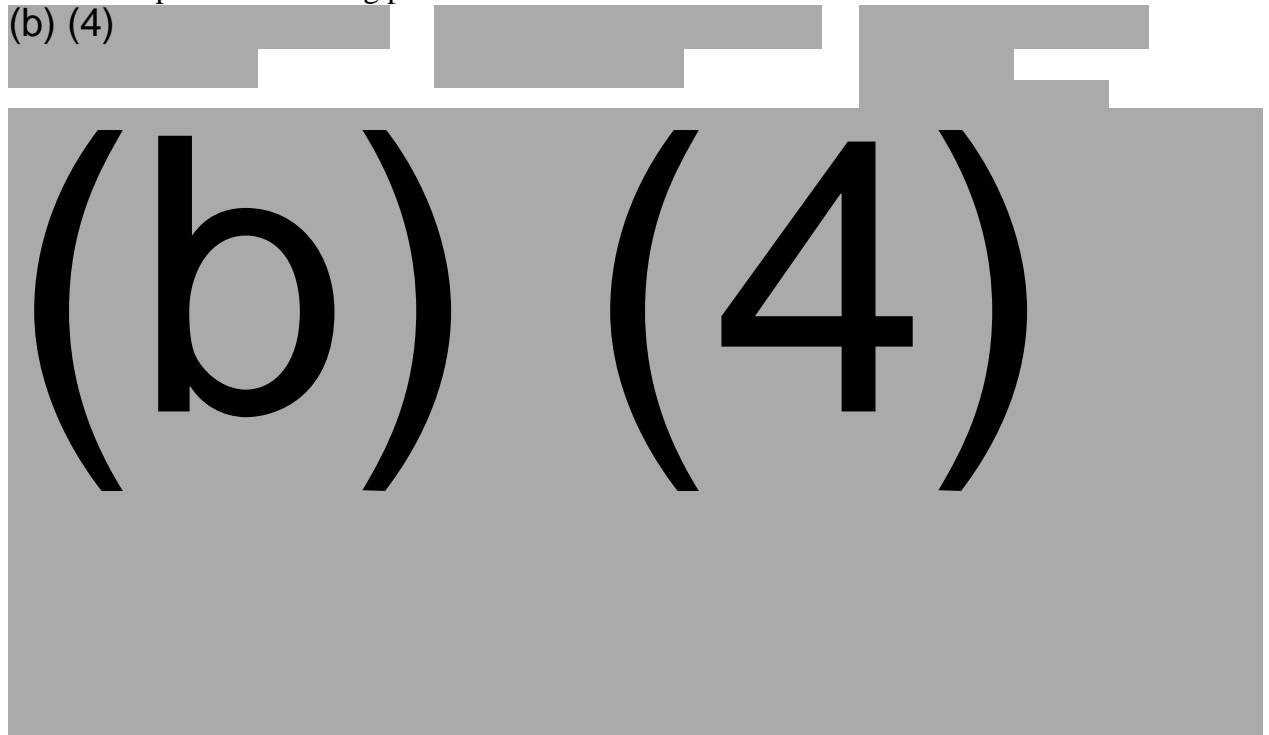
14) (b) (4)

- Real time stability data was collected and showed that (b) (4) was all above (b) (4) through 12 months.
- Stress condition: All results met with specifications.

15) Sterility

All passed for testing period in real time and stress conditions.

(b) (4)



4. CONCLUSION

- a) The raw materials is appropriately documented and controlled.
- b) The starting material and drug substance are stable under pre-defined storage condition.
- c) The final product is found to be unstable due to the OOS result appeared at 9 month for one package lot (b) (4). Sponsor stated it has the same issue as for BIVIGAM, based upon the fact that BIVIGMA's recent lot (Lot (b) (4)) has the same issue. Please note that the particulates associated with the original BLA for BIVIGAM were fiber or glass like particles and appeared to be transient, which is different from the current issue associated with RI-002, which is (b) (4) and persistent. The justification provided by sponsor was deemed to be unacceptable and the root cause is recommended to be identified (please see CR item in recommendation section).