



**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**)

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Applicant: ADMA Biologics, Inc.

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

Subject: Final Review: Original BLA Class 2 resubmission - Product Stability

RECOMMENDATION

Approval with the following PMC:

1. ADMA commits to submitting information on the ongoing stability study, SP-BK-3092, annually as a “Postmarketing Commitment – Status Update”. The final stability reports will be submitted as a “Postmarketing Commitment – Final Study Reports” by June 30, 2020. ADMA will also report any confirmed out-of-specification results at the recommendation storage condition from the stability monitoring to the Agency within 45 days of the event(s).

EXECUTIVE SUMMARY

In this Original BLA Class 2 resubmission, four types of storable materials, produced using the current manufacturing process, were tested for their stabilities (table below in this section). The proposed storage conditions for individual materials were found to be acceptable.

Up to 9 months stability data for Drug Product are available. There was no (b) (4) Particles were found at this stage and the level of subvisible particles measured using (b) (4) method did not show increasing trend over time. Statistical analysis of the stability indicating parameters for the new conformance lots indicated they were comparable to clinical and previous conformance lots. It is important to continue monitoring the Drug Product stability up to 24 months, especially for “Appearance”, visible (b) (4) Particles”, noticed in the first clinical lot at 9 months and beyond. A PMC is proposed for this purpose.

This original BLA resubmission is therefore recommended for approval, based upon the review of assigned product stability section.

Materials	Proposed by Sponsor	Recommended by Agency
(b) (4)	(b) (4)	Acceptable
		Acceptable
		Acceptable
Drug Product (Final Container)	2 - 8 °C for up to 24 months	Acceptable

BACKGROUND

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 and adolescents. During manufacturing of RI-002, (b) (4) , can be stored for certain period of time. RI-002 contains 90-110 g/L protein, of which $\geq 96\%$ 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.

This original BLA submission was issued a Complete Response (CR) Letter on July 29, 2016. One of the CR items (#14) was related to the product stability:

#14: 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.

CMC REVIEW SUMMARY

1. This memo is limited to the review of the CR response to the stability section.

- The response to the CR Letter was received on Sept 28, 2018 (125590/0.42).
- Stability Updates were requested and received on Dec 20, 2018 and Feb 22, 2019, respectively (125595/0.46 and 0.50).
- Additional information was requested and received on March 12, 2019 and on March 18, 2019, respectively (125595/0.55 and 0.59).

2. ADMA's response to FDA CR item #14

ADMA stated that they have conducted thorough investigation on the (b) (4) particles at 9 months and concluded that inadequately controlled manufacturing process coupled with stressors inherent to the manufacturing process were likely contributing to the formation of visible particles in the 9 months samples. Development studies were performed to evaluate the pathway for the optimization of the product. The manufacturing changes and enhanced procedural and engineering controls were implemented, review of which were deferred the Process Validation reviewer (Lilin Zhong, Biologist). This review will mainly focus on the assessment of three storable intermediates' as well as drug product's stabilities, produced using the current manufacturing process.

a) (b) (4)

(b) (4)

b) (b) (4)

c) Drug Product: - The proposed shelf life is 24 months at the storage of 2- 8 °C. Final product is supplied in a 50 mL (b) (4) Borosilicate Serum Vial/20 mm finish stopper, (b) (4) clinical lots, (b) (4) additional lot manufactured in 2016, and (b) (4) new conformance lots were placed under stability studies (table 1 in Appendix).

1) The results are:

- Clinical lots: (b) (4) lots, except for the one with (b) (4) particulates (b) (4), were continued to be monitored for the long term (5±3 C; 24 months), accelerated (b) (4) studies. All the studies have been completed, and the results from the real-time stability study met the stability specifications.

- Additional lot (b) (4): this lot was manufactured in 2016 and placed on real time (24 months) and accelerated (3 months) stability studies. All the real time results met the specifications.
 - Conformance lots: (b) (4) lots manufactured using the optimized process were placed under both real time and accelerated stability studies. Currently up to 9 months stability data are available. All the real time results met the specifications. For the accelerated stability study, there was (b) (4) documented in deviation DEV18065 (review of deviation is deferred to DMPQ reviewer). This single event doesn't appear to have impact on product stability.
 - ADMA also performed (b) (4) assays for conformance lots in order to monitor the product stability. The results showed that there were no increasing trends noticed for subvisible particles (Particulate Matters) measured by either method (table 2). As the results for Particulate Matters at either size were well below the requirements of (b) (4) and has been tested for lot release, it is recommended that the specifications be revisited after manufacturing of (b) (4) batches (consulted Eva Marszal, Biologist; this will be covered by Lilin Zhong, Biologist). *These results provide certain confidence that there may not have increased particles in the new conformance lots.*
- 2) Statistical analysis - to determine if certain stability indicating parameters were comparable, reviewer analyzed the up-to-9 months real time as well as accelerated stabilities data from all clinical, previous conformance, and current conformance lots. For trending analysis, the individual parameter was assigned one of three stability models, based on the nature of each tested quantitative parameter: i) Separate Intercept, Separate Slope (SISS) where both intercepts and slopes are statistically different among lots; ii) Separate Intercept, Common Slope (SICS) where lot intercepts are statistically different among lots, but lots have a common slope; iii) Common Intercept, Common Slope (CICS) where neither the intercepts nor the slopes are statistically different among lots. Common slope models, either CICS or SICS, would indicate the parameter is comparable between conformance lots and clinical lots, and a model of SISS would indicate the parameter is not comparable among these the batches. For qualitative parameters, no statistical analysis was performed.

The results are:

- A SICS model was applied to Anti-Measles antibody, Fragments, and a CICS model was applied to (b) (4), indicating the new conformance lots are comparable to the clinical and previous conformance lots.
- No trend was analyzed for other parameters as all results are well beyond the pre-defined specifications and/or due to high variation of the assay (b) (4)

Additional information requested and received on Dec 20, 2018 (125595/0.46)

FDA Query 1. Please provide an update on your ongoing stability studies.

ADMA's response: the stability data for Drug Substance and Drug Product were provided.

Reviewer's comment: ADMA provided completed stability study for Drug Substance and up to 6 months stability results for Drug Products.

Additional information requested and received on Feb 22, 2019 (125595/0.50)

FDA Query 1. Please provide an update on your ongoing stability studies and indicate when the 12 months stability data for Lot (b) (4) will become available.

ADMA's response: ADMA provided up to 9 months stability data and indicated that the 12 months stability data for the first conformance lot (b) (4) will be available by May 15, 2019.

Reviewer's comment: Lot (b) (4) will reach 12 months' time-point on (b) (4) and will not be available to review at this review cycle. It is critical to continue monitoring the product stability, especially at 9 months and beyond for (b) (4) Particulates", visible particles existed in the first clinical batch. A PMC is therefore generated to cover this (See PMC in recommendation section).

Additional quality information requested and received on March 12, 2019 (125595/0.55):

FDA query 1: regarding the updated stability data received on Feb 22, 2019, please address the following issues and/or questions:

- a) *For the parameter "Particulate Matter by (b) (4) the unitage used for three conformance batches (particles/mL) is different than the one used in Batch Analysis (particles/container). Please verify which one is correct and update the data accordingly.*
- b) *For the parameter (b) (4), there is a dramatic increase in the particulates levels at all different sizes for lot (b) (4) at the 9 months timepoint compared to other time points. Please explain and indicate if any investigation has been conducted. In addition, the results from "Particulate Matter by (b) (4) did not show any increase of the particulates, especially at (b) (4), which appears to be contradictory to the ones obtained from (b) (4). Please explain.*
- c) *Please provide a copy of deviation investigation report for DEV 18065, regarding the foreign particle found in a single vial for Lot (b) (4) at the (b) (4) storage condition, 2 months time-point. If it has been already submitted, please indicate its location in eCTD.*

ADMA's response:

- a) The correct unitage for Particulate Matter by (b) (4) is Particles/container, and the files were updated accordingly.
- b) The (b) (4) data is collected for information only and has not been fully evaluated for the potential to be used as stability indicating. The root cause could be the handling approach of the samples using aliquots from the stability vial rather than unopened vial as required by (b) (4).
- c) The final deviation report is provided.

Reviewer's comment: The (b) (4) assay is generally deemed to be more accurate assay than (b) (4) assay. Typically, either (b) (4) can be chosen by a sponsor to monitor the

subvisible particles. The final deviation report detailed the identification of the metal particle found in the stability vial. DMPQ reviewer (Silvia Wanis and Anthony Lorenzo) was notified and they stated that the issue was associated with Visual Inspection and will be reviewed and handled by DMPQ. The review of it is therefore deferred to DMPQ reviewer.

Additional quality information requested and received on March 18, 2019 (125595/0.59):

FDA query 1: Please revise the "Post-Approval Stability Protocol and Stability Commitment" to indicate that the first batch manufactured each year will be placed on stability monitoring, to ensure a random selection of annual stability lot.

ADMA's response: The protocol was updated to commit placing the first batch on stability monitoring.

Reviewer's comment: The response is acceptable.

FDA query 2: Please verify if a correct unitage has been used for (b) (4) in your stability dataset. Please update the data accordingly if any correction needs to be made.

ADMA's response: The unitage is accurate.

Reviewer's comment: the response is acceptable.

Appendix

Table 1. Drug Products Lots Placed on Stability:

	Fill Lot	Package Lot	Stability start date	(b) (4)	Target 5 ± 3°C Time Point Completed
Clinical lots	(b) (4)				24
					24
					24
					24
					24
					24
Additional lot					24
Conformance lots					9
					9
					9

* Lot with visible particles starting at 9 months at the storage of 2-8 °C, not included in the study.

Table 2. Particulate Matter by (b) (4)
Real Time condition (2-8 °C)

(b) (4)
