



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

July 29, 2016

Our STN: BL 125590/0

**BLA COMPLETE RESPONSE**

ADMA Biologics, Inc.  
Attention: Ms. Diane P. Myers  
Malvern Consulting Group, Inc.  
490 Lapp Road  
Malvern, PA 19355

Dear Ms. Myers:

This letter is in regard to your biologics license application (BLA) for Immune Globulin Intravenous (Human) manufactured at your Boca Raton, Florida location and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of information submitted in the amendment dated July 25, 2016. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Control, Manufacturing, and Chemistry

Inspectional Issues:

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

Review Issues:

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 at 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 (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 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.
12. Your product labeling has not been finalized which requires further negotiations before it can be completed.
13. For the Identity testing of RI-002, you proposed to develop a method SOP which will be based on the Identity test method that Biotest Pharmaceuticals Corporation (BPC) is using for Nabi-HB (SOP LAB3014).

- a. Please provide your method SOP for the Identity testing of labeled RI-002 final container product lots, which should include details on which positive and negative controls will be used, how the dilutions of test samples and controls will be prepared, what the positive result cut-off will be (and how it was determined), and a section on valid tests and retesting.
  - b. Please validate your proposed method according to ICH/FDA guidelines on analytical method validation (e.g., testing a sufficient number of labeled product lots of RI-002, Nabi-HB, and other BPC products, if possible) and provide the method validation results.
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 protein 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.
15. For (b) (4), please reevaluate your process based on validated robustness studies and update the specification. For (b) (4), please reevaluate your process based on validated robustness studies and update the specification.
16. You have presented the results of the intermediate precision study as evidence of robustness of the (b) (4) Assay Test Method for IGIV Drug Product. This data is insufficient to demonstrate method robustness. Please provide data to evaluate effect of small deliberate changes of critical method parameters, such as reagent concentration, incubation time, etc. in order to demonstrate method robustness.
17. The validation of the (b) (4) Assay for procoagulant impurity, coagulation (b) (4) was deficient and the proposed specifications for this assay were not justified by the impurity characterization studies. Your assay comparability investigation demonstrated a disagreement between the (b) (4) Assay and an (b) (4) method, a (b) (4) assay, for the detection of (b) (4). Since both methods were calibrated using the same (b) (4) standard, the discrepancy may indicate the presence of additional impurities detected by only one of these methods or the sensitivity of the (b) (4) Assay to product matrix components (immune globulin protein and excipients). Please investigate the sources of the observed discrepancy between the two methods. The investigation should include, but not be limited to, a side-by-side analysis by both assays of all available Drug Product (DP) lots (to investigate manufacturing consistency), with at least (b) (4) DP batches spiked with the purified (b) (4) (to investigate (b) (4) recovery and address effects of matrix), as well as stability studies of representative DP batches. Please consider changes to the analytical conditions of the (b) (4) test that may minimize the discrepancy, including the development of a product-specific standard of (b) (4) using a matrix

representative of the DP. The product-specific standard of (b) (4) should be calibrated against the current international standard for (b) (4) and placed on a stability monitoring program.

18. Regarding Lot Release Protocol template:

- a. Throughout the document, please add an additional column to each of the tables 1-5, 7, and 9 to indicate Test Date for each test.
- b. For Table 5 (Potency), please remove the test for (b) (4) (entire row).
- c. For Table 6 (Sterility), please add Result and Specification below the table.
- d. For Table 8 (b) (4) Pyrogen), please add Specification.

Pharmacovigilance/Epidemiology

19. We reserve comment on the proposed pharmacovigilance plan until the application is otherwise acceptable.

Labeling

20. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

For PDUFA products, please submit your meeting request as described in our guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*, dated May 2009 and in CBER's *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. These documents are available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf> and <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Procedures/SOPPs/ucm079448.htm>, respectively. Both documents may also be requested from the Office of Communication, Outreach, and Development at (240) 402-8020.

We acknowledge receipt of your amendment dated July 25, 2016. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross-reference applicable sections of the

amendment dated July 25, 2016, in your complete response to this letter and we will review those sections as a part of your complete response.

### **PDUFA V APPLICANT INTERVIEW**

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V (“the Program”). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Yu Do, at (240) 402-8343 or [Yu.Do@fda.hhs.gov](mailto:Yu.Do@fda.hhs.gov).

Sincerely,

Jay Epstein, MD  
Director  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research