



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

To: STN: 125590/0

From: Lilin Zhong, Biologist, CBER/OBRR/DHRR

Through: Michael Kennedy, Team Lead, CBER/OBRR/DHRR

CC: Yu Do, OMPT/CBER/OBRR/RPMS

Applicant: ADMA Biologics, Inc.

Product: Immune Globulin Intravenous (Human), 10% Liquid
Proposed Brand Name: ASCENIV

Subject: Executive Summary and Final Review - Original BLA Resubmission – Process Validation – Responses to Complete Response Letter dated 29-JUL-2016

Executive Summary

The purpose of this submission is to seek approval for the resubmission of Biologics License Application (BLA) for an Immune Globulin Intravenous, (Human) (IGIV) 10% Liquid, ASCENIV (RI-002) from ADMA Biologics Inc. The Complete Response Letter was issued on July 29, 2016 for the original BLA. This review covers the process validation section (excluding equipment and facilities) and batch record provided in the resubmission and relevant information from the original BAL submission.

In addition to (b) (4) as filling facility of drug product, ADMA has added a second contract filling site, (b) (4) ADMA validated the filling site (b) (4) and three conformant lots were produced at (b) (4) using current process.

In general, approval is recommended for process validation aspect of the resubmission with following Post Marketing Commitments that has been agreed by ADMA:

1. ADMA commits to implementing the alert limit of (b) (4) for the (b) (4) prior to the manufacture of the next lot of ASCENIV, 10% IGIV. ADMA will report the implementation as a “postmarketing commitment status update” by April 30, 2020.
2. ADMA commits to reporting the results of bioburden testing of (b) (4) for manufacturing of future lots of ASCENIV, 10% IGIV as a “Postmarketing Commitment – Status Update”, with the final report submission date of April 30, 2020.
3. ADMA commits to conducting a comprehensive study of (b) (4) of ASCENIV, 10% IGIV, using the samples held at (b) (4). Both samples will be tested for (b) (4) to generate real-time

concordance data. The final study reports will be submitted as a “Postmarketing Commitment – Final Study Report” by April 30, 2020.

4. ADMA commits to resetting the lot release specification for (b) (4) batches using the approved manufacturing process.

Background Summary

ADMA Biologics Inc. submitted a BLA for RI-002. RI-002 is a 10% human immunoglobulin intravenous. The proposed indication of RI-002 is intended for the treatment of primary immunodeficiency diseases (PIDD). The initial submission received a Complete Response in 2016. This is the resubmission with updates according the CR letter from 2016.

Dr. Pei Zhang (LPD/DHRR/OBRR) is the chair of this BLA submission. My review will focus on the Process Validation section and batch records of this BLA.

Information Requests and ADMA responses:

FDA IR #1 (January 2019): A complete deviation list and details regarding each deviation in the batch records.

ADMA Response (March 2019):

The requested list of deviations (Attachment 1) which includes details regarding each deviation in the batch records is attached.

Reviewer’s comments: Among the deviation listed in Attachment 1, there are two require further investigation:

1. *Deviation 18012: The result of Particulate Matter, RI-002 50mL Unlabeled Vial, Batch (b) (4) is out of specification. The root cause ADMA provided is: Based on the (b) (4) investigation it was concluded that the root cause of the OOS was (b) (4) in the sample solution interfering with the (b) (4). Samples were retest with passing result.*
It is concluded as acceptable. The (b) (4) occurring is only impact one sample and not all the samples from the same lot or other lots. Retesting with passing result assured that it is not a prevailing failure of any procedure of equipment.
2. *Deviation 18065 (OOS18013): RI-002 Lot (b) (4) incoming inspection appearance failure of one unacceptable vial. (b) (4) observed. These particles were found to be (b) (4) particles. It may be from (b) (4) components (b) (4) of the last (b) (4). This is after (b) (4) 100% visual inspection followed by AQL=(b) (4) inspections to ANZI/ASQ Z1.4 “Sampling Procedures and Tables for Inspection by Attributes”. Any OOS particles which should have been pointed out, however, has not.*
DBSQC reviewer concluded that this deviation is not a major concern due to it’s a single event and the second 100% visual inspection is sufficient to making sure no vial would contain this kind of particles as incoming vials from (b) (4)
Dr. Yonggang Wang while reviewing stability studies data, noticed that there are (b) (4) particles found in stability samples. After consulting with Dr. Ewa Marszal, PMC #4 was conveyed to ADMA and agreed upon.

FDA IR #2 (January 2019): All batch record comment forms related to the batch records.

ADMA Response:

All batch record comment forms related to the drug substance batch records are included with this submission. Comments for drug product batches are included in the batch records for lots (b) (4)

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Reviewer's comments: Acceptable.

FDA IR #3 (January 2019): Please clarify if samples taken for (b) (4) testing are (b) (4) prior to testing.
ADMA Response:

The RI-002 (b) (4) samples that are stored (b) (4) prior to testing for (b) (4) are from the (b) (4) (Table 1). (b) (4) data obtained from the (b) (4) samples are intended solely for trend analysis of fractionation process control and consistency. Since the impact of (b) (4) (if any) on (b) (4) of each sample type should be the same each time a sample was stored (b) (4), it was not expected to affect the interpretation of relative process trend observations over time.

(b) (4) samples taken from purification steps of the IGIV purification process are not stored (b) (4) (Table 2). These samples are tested (b) (4) (i.e. (b) (4) results from purification samples are used to confirm (b) (4) steps, monitor process control, and assure the IGIV product meets its specifications for (b) (4). ADMA recognizes that absolute (b) (4) results are necessary for appropriate control of the purification process steps and of final product material.

(b) (4)

(b) (4)

In order to determine the effect of (b) (4) in each of the fractionation samples in Table 1, ADMA commits to conducting a post-approval spiked recovery study with (b) (4) samples from RI-002. To evaluate the impact of batch variations on the results, the study will be conducted with (b) (4) batches of RI-002 (b) (4) samples.

In parallel to this comprehensive study of (b) (4) of RI-002, ADMA will collect (b) (4) samples of each of the (b) (4) given in Table 1. (b) (4). Both samples will be tested for (b) (4) to generate real-time concordance data.

ADMA commits to using the results of (b) (4) testing of (b) (4) for manufacturing of RI-002 lots until the comprehensive (b) (4) recovery studies are completed and sufficient concordance data from real-time (b) (4) samples have been collected.

The current acceptance criteria for (b) (4) are shown in Table 3. Because these (b) (4) limits were established based on the analysis of (b) (4) samples, they might not be sufficiently accurate for (b) (4) samples. Of particular concern are the current limits on (b) (4).

Therefore ADMA respectfully requests to widen the (b) (4) action limit on those (b) (4)

(b) (4) limit will be kept as an alert limit. ADMA commits to re-evaluating the limits on each of these fractionation intermediates when the (b) (4) study data are completed. In summary, ADMA commits to using the results of the (b) (4)

Table 3:

(b) (4)

ADMA will evaluate the results from (b) (4) samples as part of the current process trending SOP PRD3008 (Trending of the IgG Manufacturing Process) and will re-establish the (b) (4) specification limits for each fractionation intermediate in Table 1 once a statistically significant number of results are obtained.

Whether (b) (4) testing is performed on (b) (4) samples of (b) (4), there should be no risk to RI-002 product quality or safety because all IGIV in-process and final product produced (b) (4) are tested for (b) (4) using samples that are not (b) (4)

Reviewer's comments: (b) (4) testing samples could be compromised by (b) (4) even it's only for monitoring the trend at (b) (4) process. To ensure the testing results from (b) (4) samples can be equivalent to (b) (4) samples, PMC #1, #2 and #3 in executive summary section were conveyed to ADMA and agreed upon.

FDA IR #4: QA/QC reports related to batch record.

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ADMA Response:

Please see the attached QA/QC reports related to the drug substance batch records. The reports related to the drug product batch records are included in the CoAs for lots (b) (4)

Reviewer's comments: Acceptable.

(b) (4) Filling Facility Validation

Manufacture of RI-002 is at originally Biotest Pharmaceutical Corporation (BPC) facility in Boca Raton, FL, now ADMA manufacturing facility. Filling into final container vials for the conformant lots in this submission is performed at (b) (4). Bivigam[®] production is using the same process. The same validation was submitted under Bivigam[®] and approved.

Batch records of conformant lots:

Three conformant lots were manufactured under the updated process:

(b) (4)

Numerous notes in batch records indicated deviations and additional comments which were not part of the original submission. Information requests were conveyed in January 2019 on complete list of deviation report related to manufacturing process. refer to IR/response section IR #1, #2 and #4 in this memo:

FDA IR #1 (January 2019): A complete deviation list and details regarding each deviation in the batch records.

FDA IR #2 (January 2019): All batch record comment forms related to the batch records.

FDA IR #4: QA/QC reports related to batch record.

Bivigam is another product by ADMA and (b) (4) manufacturing process as ASCENIV. By cross reference Bivigam review with Margaret Norton, and consulted with Dr. Michael Kennedy, Information request #3 was conveyed in January 2019:

FDA IR #3 (January 2019): Please clarify if samples taken for (b) (4) testing are (b) (4) prior to testing.

Review of the responses (March 2019):

1. Review of deviation report, there are issues as (b) (4) found in final vials after (b) (4) 100% visual inspection and (b) (4) from one vial. Dr. Yonggang Wang and Dr. Ewa Marszal were consulted on the particulate issue. The last PMC #4 was agreed with ADMA. (b) (4) lots using the new process would be evaluated by testing and results would be submitted to FDA for review. Tightening the release specification of particulate testing is expected with the final results of all (b) (4) lots. We initially set that the final report should be submitted to FDA by December 31, 2020. However, the deadline was removed in order to avoid confusion because the firm might not be able to produce all (b) (4) lots by December 31, 2020.
2. In ADMA's response of March 2019, the firm requests to (b) (4) action limit o (b) (4)

(b) (4) . The (b) (4) limit will be kept as an alert limit. ADMA commits to re-evaluating the limits on each of these (b) (4) when the (b) (4) study data are completed. In summary, ADMA commits to using the results of the (b) (4)

In coordination with Bivigam review, PMC #1, #2 and #3 (refer to executive summary section of this memo) were sent to and agreed by ADMA. It is to make sure the testing results of (b) (4) are comparable and alert limits of (b) (4) is in place for these (b) (4).

Appendix

1. Batch records of this submission
2. Process validation section
3. Margaret Norton Bivigam reviews
4. Yonggang Wang reviews