



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 – ADMA BLA: Process Validation

Recommendation

A Complete Response (CR) letter is recommended for this Original BLA, which should include the following CR items:

1. For (b) (4), please reevaluate your process based on validated robustness studies and update the specification.
2. For Fraction III (b) (4), please reevaluate your process based on validated robustness studies and update the specification.

Executive Summary

The purpose of this submission is the review of a Biologics License Application (BLA) for an Immune Globulin Intravenous, (Human) (IGIV) 10% Liquid, ASCENIV (RI-002) from ADMA Biologics Inc. This review covers the process validation section (excluding equipment and facilities, and virus validation).

ADMA uses the Biotest Pharmaceuticals Corporation as their contract manufacturer for RI-002 drug substance (DS) and (b) (4) as the contract manufacturer for drug product. Biotest product of Bivigam[®] process validation was included in the submission as cross-reference. Biotest uses (b) (4) for drug product manufacturing of Bivigam[®] also.

The starting material (plasma pool) actually consists of plasma from normal SP donors (b) (4)

The manufacturing of drug substance is a modified Cohn/Oncley cold-alcohol fractionation process with two added viral clearance steps: solvent/detergent treatment of

Tri-n-butyl phosphate and Triton X-100, and virus filtration of 35nm virus filter. The (b) (4)

The final product is formulated in 100-140 mM sodium chloride, 200-290 mM glycine, 0.15–0.25% polysorbate 80 at pH 4.0–4.6. The product is currently filled into 50 mL glass vials (5 g/50 mL, target volume of (b) (4) mL). The proposed shelf life of RI-002 is 24 months, stored at 2-8 °C.

Even though (b) (4) manufacturing process of Biotest Bivigam® was used for the process of RI-002, the limits of certain critical parameters, such as alcohol concentration and pH, were not set according to Bivigam® or robustness study results. Along with the issues regarding the (b) (4) specification and the (b) (4) disease indication claim, compliance issues at the Biotest manufacturing facility, a complete response (CR) letter will be issued instead of the approval of this BLA.

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).

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

(b) (4)

(b) (4)

(b) (4)

24 pages determined to be not releasable: (b)(4)