

## **Late-Cycle Internal Meeting Summary**

**Application Type and Number:** BLA, BL 125590/0

**Product Name:** Immune Globulin Intravenous (Human) [RI-002]

**Proposed Indication:** Treatment of primary immunodeficiency disease

**Applicant:** ADMA Biologics, Inc.

**Meeting Date and Time:** March 14, 2016, 2 p.m. to 4 p.m.

**Date of LCM with applicant:** April 13, 2016

**Committee Chair:** Pei Zhang, MD

**RPM:** Yu Do, MS

### **Attendees:**

#### **Review Committee**

Chair – Pei Zhang, MD

Clinical – Charles Maplethorpe, MD, PhD

Pharmacology/Toxicology – Evi Struble, PhD

CMC Specifications and Analytical Methods - Lu Deng, PhD and Maria Luisa Virata-Theimer, PhD

CMC Process Validation – Lilin Zhong

CMC Product Stability and Shelf Life - Yonggang Wang, PhD

CMC Adventitious Agent Safety Evaluation/Viral Validation – Pei Zhang, MD and Maria Luisa Virata-Theimer, PhD

DMPQ Facilities and Equipment – Jeremy Wally, PhD

DBSQC Lot Release Protocol and Testing Plan – Marie Anderson

DBSQC Analytical Methods – Lokesh Bhattacharyya, PhD

Statistics – Boris Zaslavsky, PhD

Bioresearch Monitoring (BIMO) – Haecin Chun

Epidemiology/Pharmacovigilance – Wambui Chege, MD

#### **Additional Attendees**

Jay Epstein, MD, Director, OBRR

Basil Golding, MD, Division Director, DHRR/OBRR

Mahmood Farshid, PhD, Division Deputy Director, DHRR/OBRR

Howard Chazin, MD, MBA, Division Director (Acting), DHCR/OBRR

Mitchell Frost, MD, HPRB/DHCR/OBRR

Anne M. Pilaro, PhD, TRS/DHCR/OBRR

Iliana Valencia, MS, Chief, RPMS/OBRR

Anthony Hawkins, BMB/DIS/OCBQ

Jennifer Reed, PhD, LPD/DHRR/OBRR

Dorothy Scott, MD, LPD/DHRR/OBRR

Michael Kennedy, PhD, LPD/DHRR/OBRR

Meghna Alimchandani, MD, PB/DE/OBE

Qiao Bobo, BII/DMPQ/OCBQ

John Eltermann, DMPQ/OCBQ

William McCormick, DBSQC/OCBQ

Renee Rees, PhD, TEB/DB/OBE

## **Late-Cycle (internal) meeting agenda:**

### **1. Introduction and Overview: Application/Product [Pei Zhang/Yu Do]**

ADMA Biologics, Inc. (ADMA) submitted this biologics license application (BLA) for RI-002, plasma-derived immunoglobulin product supplied as a solution for intravenous infusion and for treatment of primary humoral immunodeficiency. The product contains 10% human protein of which at least 96% is immunoglobulin G. ADMA utilizes Biotest Pharmaceuticals, Inc. (Biotest) and (b) (4) as contract manufacturers for drug substance and drug product, respectively. The raw material is isolated from source plasma obtained from normal donors (b) (4)

### **2. Substantive review issues/major deficiencies raised during review:**

#### **a. Clinical – Charles Maplethorpe**

There are qualitative and quantitative differences in adverse events reported before or after 6 months from the date of manufacture of the product lot. These time periods were chosen for this retrospective analysis because one product lot demonstrated particle formation at 9 months by visual inspection. Additionally, all references to (b) (4) should be removed from labeling and promotional materials because the submitted data do not permit evaluation of the extent to which (b) (4) in the investigational immune globulin product has contributed to safety or efficacy outcomes.

#### **b. Clinical Pharmacology – Iftekhar Mahmood**

No substantive review issues have been noted from the clinical pharmacology perspective. There are, however, some revisions that need to be made in the labeling with regard to clinical pharmacology.

#### **c. Pharmacology/Toxicology – Evi Struble**

No substantive pharmacology/toxicology issues have been identified. Animal study data included in this submission, however, are not sufficient to support (b) (4) claim. The labeling should be revised accordingly as well.

#### **d. CMC Specifications and Analytical Methods - Maria Luisa Virata-Theimer/Lu Deng**

ADMA was asked to remove any mention of (b) (4) from the package insert and drug product release specifications as this BLA is for the indication of primary humoral immunodeficiency. ADMA was and remains insistent on retaining the (b) (4) statements, and provided a justification on February 03, 2016 (Amendment 22) for our review.

ADMA's proposed identity test (b) (4) and its specification ("(b) (4) for RI-002 are not in compliance with requirements of 21 CFR 610.14. The requirements state, "The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory." ADMA's proposed identity test and its specification for RI-002 are the same as those of other Biotest products (i.e., Bivigam and Nabi-HB), which are processed in the same Biotest QC testing laboratory.

ADMA will soon be informed of our refusal to accept the (b) (4) labeling and specification. Licensure for an (b) (4)-related indication would require demonstration of clinical benefit in the target population and is not based on outcomes from a surrogate endpoint. ADMA did not provide safety and efficacy data in the target population (i.e., patients at risk for or with severe (b) (4)).

**e. CMC Product Stability and Shelf Life - Yonggang Wang**

The first clinical lot of RI-002 manufactured in 2012 did not pass a visual inspection at 9 months of storage at 2 to 8 °C, and no root cause has been identified.

This original BLA is recommended for either a Complete Response or Approval under certain conditions:

**Complete Response** – The current stability data are not adequate to support the proposed shelf life of 24 months due to out-of-specification (OOS) test results for appearance. Investigation report that identifies root cause for the formation of (b) (4) particulates in the final product container and documentation of what corrective and preventive actions have been implemented should be provided.

**Approval under certain conditions** – Approval is recommended with one of the following options:

An initial shelf life of 6 months only can be granted because of OOS test results for visual appearance at the 9-month time point. A shelf life of 24 months may be granted with the following postmarketing commitment: ADMA commits to placing all lots manufactured in the first three years after licensure on the real-time stability studies. Monitored parameters should include the “Appearance” test. The product will be tested every three months for the initial 24-month period. The results of these stability studies will then be submitted to CBER as a postmarketing commitment (PMC) submission. Interim updates should be submitted annually, while the final study report will be submitted to CBER by July 31, 2019. ADMA should report any out-of-specification results to CBER within 30 days of the event and recall promptly any product lot that fails visual inspection or other release specifications.

**f. CMC Process Validation – Lilin Zhong**

The alcohol range settings and robustness study results for RI-002 are different from those of Bivigam. The firm’s response regarding this issue was to reset most of the values, but not all.

There were some OOS test results for (b) (4) and no root cause has been identified to resolve such issue. The RI-002 Lot (b) (4) had total alcohol range of (b) (4) (dev84373), which exceeded the acceptance criterion (b) (4). This was also the lot that was found to have visible (b) (4) particulates at 9 months after manufacture (Lot (b) (4)). Please note that root cause for the particulates was unclear, but higher level of ethanol could be one of the reasons. Other lots achieved (b) (4) for the total alcohol range and satisfied the acceptance criterion.

Alcohol concentration and pH values are critical parameters to monitor during the production process for quality assurance purposes. Further studies to develop more effective process control strategies are in order.

**g. DMPQ Facilities and Equipment – Jeremy Wally**

The FDA Form 483 from inspection of the Biotest manufacturing facility, performed by Team Biologics from January 26 to March 3, has yielded 26 observations. It appears that this facility will remain out of compliance until these issues are resolved. The unresolved inspectional issues noted from the Biotest manufacturing facility would make it probable that ADMA's submission will fail the compliance check, and this non-compliance would necessitate a Complete Response letter.

**h. DBSQC Lot Release Protocol and Testing Plan – Marie Anderson**

The comments regarding ADMA's lot release protocol template (September 25, 2015; Amendment 8) were issued on February 16, 2016.

**i. DBSQC Analytical Methods – Lokesh Bhattacharyya**

The lot release test methods were clearly described, and method validations were conducted adequately. However, there are a few outstanding issues for (b) (4) assay. These include details of a laboratory investigation by ADMA Biologics, which significantly altered LOQ, assay range, assigned value of the standard, and qualification report for the standard. These issues are not expected to be major and have been brought to the applicant's attention via Information Request. The primary discipline review memo will be submitted on March 18, 2016.

For in-support testing, (b) (4) was performed with 3 lots of the drug product, which showed that the method is adequate. The results met the proposed assay validity criteria and specification limits for different molecular forms. The in-support testing for (b) (4) however, has not been completed yet due to instrument problems.

**j. DBSQC Bioburden, Sterility, and Endotoxin – Simleen Kaur**

ADMA was asked to repeat bioburden qualification for (b) (4) with evaluation of (b) (4) in accordance with (b) (4). Additionally, the procedure that they used for the bioburden qualification study (submitted in the original submission) is different from their SOP. According to their response dated February 05, 2016, ADMA plans to provide the report for this repeat bioburden qualification study by March 22, 2016.

**k. Statistics – Boris Zaslavsky**

No major issues have been identified to date. With no subjects experiencing a serious bacterial infection (SBI) during the pivotal study ADMA-003, RI-002 has achieved its primary efficacy endpoint with success criterion of 99% upper confidence bound for the observed annual SBI rate per subject  $0.066 < 1.0$ . Clarification regarding specific value and SAS program for 99% upper confidence bound was requested on March 08, 2016.

**l. Bioresearch Monitoring (BIMO) – Haecin Chun**

BIMO inspections of three clinical sites for protocol ADMA-002 have been completed to date. The copy of the two corresponding establishment inspection reports (EIR) is still pending from ORA. BIMO plans to complete a final review upon receipt and review of the pending EIRs.

The results of BIMO inspections are as follows:

Site ID	Study Site	Location	Enrolled Subjects	Form FDA-483 Issued	Final Classification*
103	Midlands Pediatrics	Papillion, NE	9	Yes	VAI
104	The South Bend Clinic	South Bend, IN	13	Yes	EIR pending receipt and review
111	IMMUNOe Health Center	Centennial, CO	10	No	EIR pending receipt and review

\* NAI = No Action Indicated or VAI = Voluntary Action Indicated

**m. Epidemiology/Pharmacovigilance – Wambui Chege**

ADMA has submitted study protocol ADMA-005, a proposed postmarketing commitment (PMC) to evaluate potential safety concerns including risks of acute kidney injury, hepatic dysfunction, and hypotension. The protocol is currently under review, and we may request information regarding any potential deficiencies identified or clarifications required in the course of the protocol review. Of note, the PMC study proposed has not been incorporated into the current pharmacovigilance plan (PVP). If ADMA plans to include the study in the PVP, we may request submission of an updated version of the PVP for review. The safety data reviewed thus far do not substantiate a need for postmarketing requirement (PMR) or a risk evaluation and mitigation strategy (REMS).

**3. Review of upcoming timeline/deadlines [Pei Zhang or Yu Do]**

Late-Cycle meeting package to applicant: April 01, 2016  
Late-Cycle meeting (teleconference) with applicant: April 13, 2016  
Complete discipline review both primary and secondary: March 18, 2016  
PeRC Meeting: May 18, 2016  
Inform OCOD (RPM): April 29, 2016  
SSE/SBRA and Draft PI to Division Management (Chair): June 07, 2016  
Draft Approval Letter (RPM): June 14, 2016  
Draft PI and Information Request to Jennifer (Chair): June 14, 2016  
SSE/SBRA+ PI + Approval Letter to OBRR Management: June 21, 2016  
Comments from OBRR Management: June 24, 2016  
Meeting with OBRR Management: June 30, 2016  
Complete package to RPM (Chair): July 08, 2016  
Final PI to the applicant (RPM): July 14, 2016  
Finalize package (RPM): July 21, 2016  
Inform Jennifer - ADD (RPM): July 22, 2016  
Route for signatures (RPM): July 25, 2016  
OBRR Management Signature: July 29, 2016  
T-x Date: July 15, 2016  
Target ADD: July 29, 2016

4. Assess status of the review, including plans for completing outstanding discipline reviews and any other remaining issues [**Review Committee**]

Please see Item 2 for details.

5. There is no need at this time to present this application before the Blood Products Advisory Committee.
6. There is no anticipation of a REMS (risk evaluation and mitigation strategy) or a PMR (postmarketing requirements).
7. Reach agreement on meeting materials. [**Pei Zhang and Review Committee**]

The Late-Cycle meeting package will be prepared by Yu Do and routed to the meeting participants for review.

8. The regulatory project manager will meet separately with the committee chair and management to reach agreement on agenda items to be discussed during the Late-Cycle meeting with the applicant. [**Yu Do, Pei Zhang, Michael Kennedy, and Dorothy Scott**]

Drafted: Yu Do / March 14, 2016  
Revised: Pei Zhang / April 15, 2016  
Reviewed: Charles Maplethorpe / April 14, 2016  
Revised: Dorothy Scott / April 15, 2016