

## Mid-Cycle 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:** January 07, 2016, 2 p.m. to 4 p.m.

**Committee Chair:** Pei Zhang, MD

**RPM:** Yu Do, MS

### Review Committee:

Chair – Pei Zhang, MD

Clinical – Charles Maplethorpe, MD, PhD

Clinical Pharmacology – Iftekhar Mahmood, PhD

Pharmacology/Toxicology – Evi Struble, PhD

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

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

DMPQ Facilities and Equipment – Michael Vardon

DBSQC Lot Release Protocol and Testing Plan – Marie Anderson

APLB Labeling – Alpita Papat, PharmD

DBSQC Analytical Methods – Lokesh Bhattacharyya, PhD

DBSQC Bioburden, Sterility, and Endotoxin – Simleen Kaur

Statistics – Boris Zaslavsky, PhD

Bioresearch Monitoring (BIMO) – Haecin Chun

Epidemiology/Pharmacovigilance – Wambui Chege, MD

### Additional Attendees:

Jay Epstein, MD, Director, OBRR

Ginette Michaud, MD, Deputy Director, OBRR

Basil Golding, MD, Division Director, OBRR/DHRR

Paul D. Mintz, MD, Division Director, OBRR/DHCR

Boguang Zhen, PhD, Branch Chief, TEB/DB/OBE

Patricia Holobaugh, Branch Chief, BMB/DIS/OCBQ

Lisa Stockbridge, PhD, Branch Chief, APLB/DCM/OCBQ

Iliana Valencia, MS, Chief, RPMS/OBRR

Anthony Hawkins, BMB/DIS/OCBQ

Jennifer Reed, PhD, LPD/DHRR/OBRR

Michael Kennedy, PhD, LPD/DHRR/OBRR

Meghna Alimchandani, MD, PB/DE/OBE

This Mid-Cycle meeting began by providing the attendees with an opportunity to introduce themselves. Pei Zhang, the committee chair, then gave a brief overview of the submission.

## **Report and Discuss:**

### 1. Reviewer Reports:

#### Clinical

[Charles Maplethorpe]

According to CMC reviewer's report on December 21, 2015, at least one product lot has been reported to form visible particles within the period of 6 to 9 months after the date of manufacture. This prompted a need to analyze the adverse event database for qualitative and quantitative differences in adverse events reported within and after 6 months of the product manufacture. Information requests will be submitted for stability data for every product lot including those not used in the clinical trial and to perform similar analyses using adverse event database since the Phase 3 Trial and taking into account the product age (i.e., product administered within or after 6 months of its manufacture date) and product lot used immediately before observation of a reported adverse event. The package insert will also have to be revised in accordance with proposed changes. The clinical review is planned to be completed on or before July 09, 2016.

#### Epidemiology/Pharmacovigilance

[Wambui Chege]

Of particular concern are the potential risks of hypotension and renal and hepatic failures associated with BIVIGAM, an IGIV product produced by the same manufacturer as that of RI-002, due to Polysorbate 80 in the final formulation. Additionally, there is evidence in the clinical safety database of potential cases of hypotension and hepatic dysfunction following the administration of RI-002. Although acute renal failure is listed in their pharmacovigilance plan (PVP) as a potential safety concern, the applicant did not include liver dysfunction or hypotension in the PVP and made no proposals for postmarketing study or safety surveillance plan to evaluate these safety concerns. Therefore, OBE/DE may request information regarding episodes of hypotension and hepatic or renal dysfunction during the clinical trial ADMA-003 and proposal of additional pharmacovigilance activities to address these safety concerns. The primary review for epidemiology will be completed in April 2016.

#### Pharmacology/Toxicology

[Evi Struble]

No substantive issues of pharmacology/toxicology have been identified at this time, which might preclude an approval. Studies BE-008-91 and BE-009-91 are currently under review. The primary review for pharmacology/toxicology will be completed by March 04, 2016.

#### Clinical Pharmacology

[Iftekhar Mahmood]

No substantive issues of clinical pharmacology have been identified at this time, which might preclude an approval or impact the review timeline. The primary review for clinical pharmacology is still ongoing and will be completed by February 15, 2016.

CMC Specifications and Analytical Methods [Maria L. Virata-Theimer/Lu Deng]  
RI-002 bears a great resemblance to BIVIGAM in terms of specifications and analytical methods for Drug Substance and Drug Product testing. A distinct difference between the two products is the (b) (4) test for RI-002, which will be performed at (b) (4). A few issues regarding (b) (4) assay have been identified and will need to be addressed by the applicant. An information request regarding these issues is ready to be submitted. The primary review for this discipline section will be completed by March 04, 2016.

CMC Process Validation [Lilin Zhong]  
The ranges of alcohol concentration for fractionation set for operation fall below the levels determined to be optimal in the robustness study report. This discrepancy, along with other issues regarding the process validation robustness studies, needs to be explained and clarified via information request.

No other substantive issues have been identified at this time. The primary review for this discipline section will be completed by March 04, 2016.

CMC Adventitious Agent Safety Evaluation [Pei Zhang/Maria L. Virata-Theimer]  
No substantive issues have been identified in this regard. The primary review for this CMC section will be completed by March 04, 2016.

CMC Product Stability and Shelf Life [Yonggang Wang]  
Visual appearance and detection of measles antibody are two primary factors impacting the stability of this product. Stability update with these two assessments has been requested.

The first clinical lot manufactured in 2012 failed a visual inspection test after 9 months of storage at 2 - 8°C with no root cause identified. The adverse events associated with this particular lot will be analyzed for further consideration by clinical reviewer. (b) (4) batches, manufactured in 2013 and 2014, however, did not have any visual appearance issues.

The investigation report of the BIVIGAM Lot (b) (4) for out-of-specification visual appearance events that occurred at the 12-month time point will be requested for review. This BIVIGAM lot was manufactured at the same time and has the similar issue as the first clinical lot does.

The proposed (b) (4) filter for infusion is not recommended because it may retain the precipitated IGIV, thereby reducing the actual amount of IGIV being infused.

The primary review for product stability will be completed by March 04, 2016.

DMPQ Facilities and Equipment [Michael Vardon]  
DMPQ's review of the manufacturing process for RI-002 includes the drug substance operations at the Biotest Pharmaceutical Corporation (Biotest) facility in Boca Raton, FL,

and drug product operations at the (b) (4) with a focus on the facilities, equipment qualification, cleaning and sterilization, container closure integrity testing, and filling and packaging operations. A warning letter was issued to the Biotest facility on November 25, 2014, and Team Biologic's follow-up inspection, during which the firm's corrective actions will be evaluated, is tentatively scheduled for January 2016. The OAI (Official Action Indicated) status for this facility will not allow DMPQ to waive pre-approval inspection at this time. Finally, there is currently an information request from January 5, 2016, for which a response is still pending. DMPQ's primary review will be completed by March 04, 2016.

Bioresearch Monitoring (BIMO) [Haecin Chun]

There are no substantive BIMO issues identified at this time. Inspection results from three clinical investigator sites (i.e., Site #103 in Papillion, NE, Site #111 in Centennial, CO, and #104 in South Bend, IN) are still pending. The BIMO review will be completed approximately 30 days after CBER receipt of each EIR (establishment inspection report) package.

DBSQC Quality, Analytical Methods, and In-Support Testing [Lokesh Bhattacharyya]

Information request regarding (b) (4) assay remain outstanding. (b) (4) assays for in-support testing are currently in progress. The primary review for this discipline will be completed by February 29, 2016.

DBSQC Bioburden, Sterility, and Endotoxin [Simleen Kaur]

Bioburden specification calculation, testing procedures, and (b) (4) results of positive controls in the qualification report, submitted on November 13, 2015, are in need of clarification. An information request will be submitted to address these issues. Otherwise, no substantive issues have been identified at this time to preclude an approval of the application.

DBSQC Lot Release Protocol and Testing Plan [Marie Anderson]

The Lot Release Protocol (LRP) template has been reviewed and routed to CMC and PRB reviewers for further comments. The request for lot release samples and comments on the LRP template may be issued to ADMA Biologics around January 29, 2016. The draft testing plan is currently under review by Pei Zhang, William McCormick, and Lokesh Bhattacharyya.

Statistics [Boris Zaslavsky]

With no subjects experiencing a serious bacterial infection (SBI) during the pivotal study ADMA-003, RI-002 achieved its intended primary efficacy endpoint with success criterion of 99% confidence bound for the observed annual SBI rate per subject <1.0. Therefore, no substantive statistical issues have been identified to report at this time. The primary review for statistics will be completed by March 18, 2016.

2. No discipline review letters will be issued at this time.

3. If the application will be discussed at an Advisory Committee meeting, identify potential issues for presentation.

A decision to present before the Blood Products Advisory Committee (BPAC) has not been made yet. Potential issues for discussion at the BPAC meeting may or may not need to be identified depending upon the applicant's response to pending information requests. BPAC meeting, if needed, should be scheduled no later than 3 months before the action due date (i.e., April 29, 2016).

4. The review committee identified no need for Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs), or Risk Evaluation and Mitigation Strategies (REMS) at this time.
5. National Drug Codes (NDCs) have not been uniquely assigned yet for product and packaging by the applicant. [Yu Do]
6. The recommended proper name of this product is Immune Globulin Intravenous (Human).
7. Status of GMP and BIMO inspections has been updated under Item 1 (see DMPQ and BIMO sections, respectively, for details).

### **Confirm**

8. The Data Abstraction Team (DAT) has been notified of this original BLA, and Components Information Table was obtained as a result. The committee chair was also given access to the BITS-ABC database. [Yu Do]
9. New facility information from the application has been entered into RMS-BLA. The facility information entry in RMS-BLA will be checked for accuracy and completeness. [Michael Vardon/Yu Do]
10. Lot release protocol template and sample request will be issued around January 29, 2016. The draft testing plan is still under review. [Marie Anderson]
11. Unique ingredient identifier (UNII) code has been assigned to this product on October 29, 2015 and will soon be conveyed to the applicant. [Yu Do]
12. PeRC presentation date for this original BLA is set for May 18, 2016. The regulatory project manager will work with clinical reviewer to prepare and submit PeRC forms and other review materials two weeks in advance of the scheduled meeting. The clinical reviewer will address the Agreed Initial Pediatric Study Plan and requests for partial waiver and deferral. [Yu Do]

13. The regulatory project manager will need to meet with Committee Chair separately to reach an agreement on information to be included in the Mid-Cycle Communication with the applicant. No substantive issues need to be discussed at the Mid-Cycle Communication. The Mid-Cycle Communication is only for applications that qualify under the PDUFA V Program. [Yu Do]

## **Review**

14. Pending dates of major targets and milestones:

Mid-Cycle Communications outline - January 15, 2016  
Mid-Cycle Communications - January 19, 2016  
Late-Cycle internal meeting - March 14, 2016  
Late-Cycle meeting materials - April 01, 2016  
Late-Cycle external meeting - April 13, 2016  
Advisory Committee Meeting (if needed) – April 29, 2016 (pending)  
Completion of supervisory review - June 30, 2016  
Proprietary name review - March 15, 2016  
First action due - July 30, 2016

15. Please see Item 1 for details regarding the current status of review for each discipline and inspection and EIR.

16. A labeling review meeting for RI-002 should be scheduled on or after April 29, 2016.

## **Action items:**

The Mid-Cycle Communication (MCC) has been scheduled for January 19, 2016.

Meeting to reach agreement on information to share during MCC will be held before January 15, 2016. [Yu Do and Pei Zhang]

Drafted: Yu Do / January 11, 2016  
Reviewed: Pei Zhang / February 01, 2016  
Revised: Charles Maplethorpe / January 19, 2016  
Revised: Evi Struble / January 28, 2016  
Reviewed: Haecin Chun / January 11, 2016  
Revised: Michael Vardon / January 19, 2016  
Reviewed: Wambui Chege / February 01, 2016  
Revised: Yonggang Wang / January 11, 2016  
Revised: Lu Deng / January 19, 2016  
Revised: Lilin Zhong / January 19, 2016  
Revised: Maria L. Virata-Theimer / January 20, 2016  
Reviewed: Marie Anderson / February 01, 2016  
Revised: Dorothy Scott / February 08, 2016