



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL 125590/0

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

Dear Ms. Myers:

Attached is a copy of the memorandum summarizing your April 13, 2016, Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Yu Do at (240) 402-8343.

Sincerely,

Basil Golding, MD
Director
Division of Hematology Research and Review
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: Wednesday, April 13, 2016, 1 p.m. to 2 p.m., EDT
Meeting Location: Teleconference

Application Number: BL 125590/0
Product Name: Immune Globulin Intravenous (Human), 10% Liquid
Proposed Indication: Treatment of primary humoral immunodeficiency
Applicant Name: ADMA Biologics, Inc. (ADMA)

Meeting Chair: Pei Zhang, MD
Meeting Recorder: Yu Do, MS

FDA ATTENDEES

Lokesh Bhattacharyya, PhD, Chief, OCBQ/DBSQ/LACBRP
Qiao Bobo, PhD, Consumer Safety Officer, OCBQ/DMPQ/BII
Wambui Chege, MD, Medical Officer, OBE/DE/PB
Haecin Chun, Consumer Safety Officer, OCBQ/DIS/BMB
Yu Do, MS, Regulatory Project Manager, OBRR/RPMS
John Eltermann, RPh, MS, Director, OCBQ/DMPQ
Jay Epstein, MD, Director, OBRR
Mahmood Farshid, PhD, Deputy Director, OBRR/DHRR
Mitchell Frost, MD, Chief, OBRR/DHCR/HPRB
Basil Golding, MD, Director, OBRR/DHRR
Anthony Hawkins, Consumer Safety Officer, OCBQ/DIS/BMB
William McCormick, PhD, Director, OCBQ/DBSQ
Dorothy Scott, MD, Chief, OBRR/DHRR/LPD
Evi Struble, PhD, Research Pharmacologist, OBRR/DHRR/LPD
Jeremy Wally, PhD, Acting Chief, OCBQ/DMPQ/BII
Scott Winiecki, MD, Medical Officer, OBE/DE/PB
Pei Zhang, MD, Research Biologist, OBRR/DHRR/LPD
Lu Deng, PhD, Staff Fellow, OBRR/DHRR/LPD
Maria Luisa Virata-Theimer, PhD, Chemist, OBRR/DHRR/LPD
Yonggang Wang, PhD, Staff Fellow, OBRR/DHRR/LPD
Boris Zaslavsky, PhD, Mathematical Statistician, OBE/DB/TEB
Boguang Zhen, PhD, Chief, OBE/DB/TEB

EASTERN RESEARCH GROUP (ERG) ATTENDEES

Christopher Sese, Contractor, CDER/OSP

ADMA ATTENDEES

James Mond, MD, PhD, Chief Scientific Officer, Chief Medical Officer, ADMA
Lucy DeMario, PhD, Senior Director, Quality, ADMA
Adam Grossman, President & CEO, ADMA
Kaitlin Kestenber, Director of Program Management, Clinical Ops

Catherine MacArthur, Senior Quality Assurance Manager, ADMA
Diane P. Myers, Regulatory Consultant, Malvern Consulting Group (MCG)
Gerri Henwood, Development Consultant, MCG
Randall Mack, Development Consultant, MCG
Alex Freyer, PharmD, Development Consultant, MCG
(b) (4), Statistical Consultant
(b) (4) - Regulatory Consultant
Teresa O'Brien, Head of Regulatory Affairs, Biotest Pharmaceuticals Corporation
David Burney, VP of Quality, Biotest Pharmaceuticals Corporation

BACKGROUND

BLA 125590/0 was submitted on July 31, 2015, for Immune Globulin Intravenous (Human).

Proposed indication: Treatment of primary humoral immunodeficiency

PDUFA goal date: July 30, 2016

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on April 1, 2016.

DISCUSSION

1. Discussion of Substantive Review Issues/Major Deficiencies

- a. *Compliance issues at ADMA's contract manufacturer, Biotest Pharmaceuticals Corporation (Biotest), have yet to be resolved.*

ADMA asked what impact Biotest's compliance issues could have on the approval of this BLA and stated that Biotest had submitted responses to the observations listed in the Form FDA 483 on March 24, 2016.

FDA stated that the final decision regarding the outcome of the GMP inspection of the Biotest facility is still pending, but that this facility would need to be in compliance in order for this BLA to be approved. The Division of Manufacturing and Product Quality in the Office of Compliance and Biologics Quality was not aware of Biotest's recent submission of the responses to the observations in the FDA Form 483, as they would be processed and reviewed by a different Division within the Agency that is responsible for the GMP inspections and is separate from the review team for this BLA.

- b. *Any reference to (b) (4) should be excluded from the labeling, promotional materials, and product release specifications.*

ADMA stated that they submitted their justification regarding (b) (4) claim on February 3, 2016, and were waiting to be informed of FDA's review outcome.

FDA stated that ADMA's justification has been reviewed, but did not alter the former decision regarding (b) (4) issues.

ADMA stated that the content of this product application was based on the manufacturing scheme established and agreed upon by FDA in the previous meetings. FDA emphasized that ADMA cannot make such an implicit product claim in the absence of corresponding clinical efficacy data.

ADMA asked if it would be possible to meet separately with FDA and to seek further details and guidance in resolving the issues surrounding their (b) (4) claim. FDA agreed to grant this meeting as a teleconference with the appropriate reviewers.

- c. *The current stability data are inadequate to support the proposed shelf life of 24 months at the storage condition of 2-8 °C.*

ADMA plans to submit additional stability data that would support the proposed shelf life of 24 months at 2 to 8 °C near the end of April 2016.

2. Discussion of Additional Review Issues

- a. *The proposed identity test and its specification for RI-002 do not adequately comply with the requirements of 21 CFR 610.14.*

FDA stated that the proposed identity test should be designed to distinguish IgG of RI-002 from those of BIVIGAM and Nabi-HB.

ADMA asked if using different cap colors on the vials would be sufficient to satisfy the requirements. FDA clarified that the IgG of RI-002 has to be differentiated chemically, physically, or immunologically from those of BIVIGAM and Nabi-HB by testing the material itself. Using different cap colors on the vials is not sufficient.

- b. *No root cause of OOS (out-of-specification) test results for the precipitation/separation of (b) (4) has been identified.*

ADMA stated that the investigation regarding these OOS test results is still ongoing. The results of this investigation should be available in May 2016. Additionally, Biotest is currently working to revise their dilution scheme to decrease the variability of the alcohol concentration assay.

3. Additional Applicant Data

ADMA plans to submit a third request for the proprietary name review during the week of April 17, 2016.

4. Information Requests

Information Request dated February 16, 2016, regarding the Lot Release Protocol template

ADMA asked if it would be okay for them to submit the lot release protocol template with the (b) (4) reference intact.

FDA agreed to let ADMA submit the lot release protocol template with the (b) (4) reference included for now, pending the meeting to be scheduled for discussion of the (b) (4) issues.

5. Discussion of Upcoming Advisory Committee Meeting

This application will not be presented before the Advisory Committee.

6. Risk Management Actions (e.g., REMS)

There is no anticipation at this time that a REMS will be needed.

7. Postmarketing Requirements/Postmarketing Commitments

We have not identified any safety issues that would substantiate a need for a PMR study. The PMC protocol ADMA-005 proposed to evaluate potential safety concerns including risks of acute kidney injury, hepatic dysfunction, and hypotension is currently under review.

8. Major Labeling Issues

With the exception of (b) (4)-related items listed in 2b, there are no major labeling issues identified at this time.

9. Review Plans

Labeling review:
Pediatric Review Committee meeting, May 18, 2016

10. Applicant Questions –5 minutes

ADMA had no further questions.

11. Wrap-up and Action Items – 5 minutes

A teleconference will be scheduled between FDA and ADMA to have further discussion on the (b) (4) issues.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.