



Meeting Summary

Application type and number: BL 125590/0
Product name: Immune Globulin Intravenous (Human)
Proposed indication: Treatment of primary immunodeficiency disease
Applicant: ADMA Biologics, Inc.
Meeting date & time: June 27, 2016, 9:30 a.m. to 11 a.m., EDT
Meeting format: Face-to-face
Meeting chair/leader: Dorothy Scott, MD
Meeting recorder: Yu Do, MS

Preliminary responses: June 23, 2016

FDA participants:

Howard Chazin, MD, Director (Acting), Division of Hematology Clinical Review, OBRR
Lu Deng, PhD, Staff Fellow, Division of Hematology Research and Review, OBRR
Yu Do, MS, Regulatory Project Manager, Regulatory Project Management Staff, OBRR
Mitchell Frost, MD, Branch Chief, Hematology Products Review Branch, Division of Hematology Clinical Review, OBRR
Michael Kennedy, PhD, Biologist (Team Lead), Division of Hematology Research and Review, OBRR
Sherry Lard, PhD, Associate Director for Quality Assurance, Office of the Center Director, CBER
Rubina Madni, JD, Associate Chief Counsel for Biologics, Office of the Chief Counsel, Office of the Commissioner
Charles Maplethorpe, MD, PhD, Medical Officer, Division of Hematology Clinical Review, OBRR
Dorothy Scott, MD, Laboratory Chief, Division of Hematology Research and Review, OBRR
Evi Struble, PhD, Research Pharmacologist, Division of Hematology Research and Review, OBRR
Iliana Valencia, MS, MCPM, Chief, Regulatory Project Management Staff, OBRR
Maria Luisa Virata-Theimer, PhD, Chemist, Division of Hematology Research and Review, OBRR
Nicole Verdun, MD, Deputy Director (Acting), Office of Blood Research and Review (OBRR)
Pei Zhang, MD, Research Biologist, Division of Hematology Research and Review, OBRR
Lilin Zhong, MS, Biologist, Division of Hematology Research and Review, OBRR

ADMA Biologics, Inc. (ADMA) attendees:

James Mond, MD, PhD, Chief Scientific Officer, Chief Medical Officer, ADMA

Adam Grossman, President & CEO, ADMA

Kaitlin Kestenber, Director of Program Management, Clinical Operations, ADMA

Diane P. Myers, Regulatory Consultant, Malvern Consulting Group (MCG)

Gerri Henwood, Development Consultant, MCG

(b) (4)

Michael Druckman, JD, Regulatory Consultant, Hogan Lovells US LLP

Sari Bourne, JD, Regulatory Consultant, Hogan Lovells US LLP

Jordan Orange MD, PhD, Clinician, Pediatric Immunology, Allergy, and Rheumatology, Baylor

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Background and Objectives

During the Late-Cycle teleconference, FDA agreed to meet with ADMA for a further discussion regarding the disclosure of standardized level of (b) (4) in the package insert and as a drug product release specification. ADMA submitted a briefing package on June 6, 2016.

FDA provided its proposed responses to ADMA's questions on June 23, 2016. After reviewing the proposed responses, ADMA notified FDA on June 24, 2016, of its decision to focus the discussion on the following core themes:

1. Appropriateness or necessity of disclosure of the standardized (b) (4) of the product in the labeling.
2. Materiality of (b) (4) to the constitution of the product and the necessity of including it as a product specification.
3. Safety, and other implications, of failure to include a statement of (b) (4) and potential interactions with other products such as monoclonal antibody (e.g., (b) (4) and vaccines currently under phase 2b or 3 clinical development.

Summary of Discussion*Appropriateness of Disclosure (1) and Materiality (2) of the (b) (4)*

ADMA asserted that standardized (b) (4) of their Immune Globulin Intravenous (IGIV) product is considered to be material, and that it should be mentioned in the package insert (PI) and as a product release specification. ADMA then asked FDA for an explanation of the concerns and issues that the FDA has with regard to inclusion of (b) (4) statements in the PI and as a product release specification in seeking approval of their product for the treatment of primary immunodeficiency disease (PIDD) indication.

FDA stated that no mention of (b) (4) should be made in the PI or as a product release specification unless there is adequate clinical data or evidence to support such reference. Based

on the submitted information, it still remains unknown how clinically meaningful the standardized (b) (4) of the product is and what potential safety implications that such characteristic would pose.

FDA asked ADMA for its intent on insisting to include (b) (4) statements for the PIDD indication. The clinical data submitted were to demonstrate efficacy in treatment of PIDD patients using incidence of serious bacterial infections (SBI) as a primary endpoint. FDA noted that (b) (4) has no relevance to this primary endpoint and is not clinically meaningful for the indication of PIDD being sought by ADMA in this BLA.

ADMA stated that (b) (4) is a fundamental attribute of the product and that it should be disclosed publically in the spirit of making the product transparent in terms of description and characteristics for patients and prescribers in order for them to make an informed decision. This IGIV product is not generic and has been designed with this key feature in mind.

FDA questioned the rationale as to why patients would want to seek such information and the utility of making such a claim with no supporting evidence from the clinical data. The prescriber would also be left ambivalent and unsure of how to use this information when prescribing this product in a medical practice.

ADMA clarified that they do not intend to (b) (4) and will provide the appropriate data in this regard when it is ready for submission after completion of the ongoing study. ADMA also speculated that (b) (4) correlate with (b) (4) as well, which remains to be proven.

FDA emphasized that to make such reference in the labeling without efficacy data would be considered an implied claim, even with an explicit disclaimer. The FDA has taken the same approach toward other IGIV products; therefore, authorizing (b) (4) statements to be included in the labeling would mean running counter to that precedent and giving implicit permission to other sponsors of plasma-derived and IGIV products to follow suit in seeking to include such implied claims in their labeling.

FDA asked why ADMA had selected plasma donors with high (b) (4) in particular, as opposed to (b) (4). ADMA contended that it has some historical data which provided some supporting evidence for materiality of the (b) (4), over other (b) (4), to the IGIV product.

FDA expressed concern about ADMA's extensive use of the term "materiality" and asked ADMA for clarification on how ADMA defines this term. ADMA stated that "materiality" is established when the removal of its associated feature results in a definable consequence. ADMA admitted that the IGIV product has not yet been shown to be efficacious for the treatment of (b) (4) like (b) (4). As stated in the February 3, 2016, submission, ADMA believes that (b) (4) is material to the constitution of their IGIV product as a unique characteristic and has been standardized in the manufacturing process to be consistent in the final product.

FDA stated that the burden of proof is on the sponsor/applicant to show their product is superior over other products available in the market for the treatment of (b) (4).

ADMA spoke of the challenges involved in clearly showing a superiority therapeutic claim for biologics because of the sheer complexity of the product. Thus, ADMA considers that more importance should be placed on the manufacturing process when it comes to evaluating biologics products.

ADMA stated that there are some examples of approved plasma-derived products, such as Kcentra whose package insert (PI) describes product ingredients with no clinical trial data for each specific amount. Kcentra's PI lists Proteins C and S in the product description with no supporting clinical data. FDA countered that the example that ADMA cited is not relevant because Kcentra is a prothrombin complex concentrate (a combination of blood coagulation factors), not an immune globulin product, and Proteins C and S affect the coagulation system.

FDA stated that the reference to the (b) (4) of the product belongs under product characterization, not in the package insert or product release specifications. FDA noted its concerns related to a lack of justification of how this particular feature of the product ((b) (4)) makes a difference for the PIDD patient population.

ADMA noted that there is no concept of what difference neutralizing antibodies against diphtheria, measles, and polio in the product make for the PIDD patients either. ADMA asked why the minimum levels of neutralizing antibodies against diphtheria, measles, and polio in the IGIV product would be permitted for disclosure without supporting clinical data. ADMA also asked for the same explanation regarding IgA content of IGIV products.

FDA stated that the content of such antibodies in the immune globulin product serve as surrogates of potency as per the requirements in 21 CFR 640.104. IgA content of the IGIV product needs to be disclosed for safety reasons because it may potentially lead to anaphylactic reactions in the IgA-deficient patients.

ADMA asked for clarification on how changes in the manufacturing process for donor selection and plasma pooling should be reported to FDA.

FDA stated that ADMA needs to submit supporting data and information via a Prior Approval Supplement to report such proposed changes after approval of the original BLA.

Safety Implications of Failure to Include (b) (4) Statement (3)

In support of ADMA's argument for including information about (b) (4) in their labeling, ADMA stated they have some preliminary *in vitro* data to indicate that their IGIV product may inhibit the neutralizing ability of (b) (4) and other monoclonal antibody products against viruses and asked if these data should be submitted before the action due date. Moreover, ADMA asked if these drug interaction data, upon submission, would constitute a major amendment to extend the review clock for this original BLA.

FDA asked ADMA to submit these drug interaction data as soon as possible as they may merit a need to be posted in the package insert, possibly in a Boxed Warning or under Contraindications. There may also emerge a need to conduct a pediatric study as a result. Whether the drug interaction data would be considered a major amendment and extend the review clock remains to be determined upon review of the submitted data.

Regarding a path forward for an (b) (4) indication, FDA stated its willingness to explore the possibility of an accelerated approval mechanism. There are some distinct requirements for this pathway, such as selection of acceptable surrogate endpoints, with which ADMA must comply, but a separate meeting and submission will need to take place for further discussion of this regulatory pathway.

Closing Remarks

FDA asked ADMA to consider removing the (b) (4) statement from the package insert and product specification as the firm has not submitted sufficient data in this BLA to seek a product approval with disclosure of such information. If ADMA agrees to comply with FDA's request regarding an (b) (4) statement, FDA may soon thereafter begin a negotiation process for the final labeling. FDA asked that ADMA consider making their decision swiftly as there is not much time remaining of this BLA review cycle.

ADMA asked if FDA's preliminary responses would be subject to additional revisions as a result of this meeting.

FDA clarified that the proposed written responses, issued to ADMA on June 23, 2016, represent the FDA's official position and will not be edited further.

END