



Reference: BL 125590/0

Date: March 25, 2019

ADMA Biologics, Inc.
Attention: Mr. James Maloney
Senior Director of Regulatory Affairs
5800 Park of Commerce Boulevard, N.W.
Boca Raton, FL 33487

Dear Mr. Maloney:

Attached is a copy of the memorandum summarizing your March 6, 2019, Type C 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 as soon as possible.

Please include a reference to CRMTS #11698 and BL 125590/0 in your future submissions related to the subject product.

If you have any questions, please contact Yu Do at (240) 402-8343 or Yu.Do@fda.hhs.gov.

Sincerely,

Nannette Cagungun, MS, PD, RAC
Chief, Branch 1
Division of Regulatory Project Management
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Meeting Summary

Meeting ID: CRMTS #11698
Application type and number: BLA, BL 125590/0
Product name: Immune Globulin Intravenous (Human)
[ASCENIV]
Proposed indication: Treatment of primary immunodeficiency disease
(PIDD)
Sponsor: ADMA Biologics, Inc. (ADMA)
Meeting type: Type C
Meeting date & time: Wednesday, March 6, 2019, 1 p.m. to 2 p.m., EST
Meeting format: Teleconference
Meeting recorder: Yu Do, MS

Preliminary Responses: **March 4, 2019**

FDA Attendees:

Marie Anderson, Division of Biological Standards and Quality Control (DBSQC)/Office of Compliance and Biologics Quality (OCBQ)
Faith Barash, MD, Pharmacovigilance Branch (PB)/Division of Epidemiology (DE)/Office of Biostatistics and Epidemiology (OBE)
Deborah Belsky, MD, General Medicine Branch 1 (GMB1)/Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)/Office of Tissues and Advanced Therapies (OTAT)
Kimberly Benton, PhD, OTAT
Wilson W. Bryan, MD, OTAT
Lu Deng, PhD, Plasma Derivatives Branch (PDB)/Division of Plasma Protein Therapeutics (DPPT)/OTAT
Stephanie Donahoe, Advertising and Promotional Labeling Branch (APLB)/Division of Case Management (DCM)/OCBQ
Basil Golding, MD, DPPT/OTAT
Mahmood Farshid, PhD, DPPT/OTAT
Lin Huo, PhD, Therapeutics Evaluation Branch (TEB)/Division of Biostatistics (DB)/OBE
Michael Kennedy, PhD, PDB/DPPT/OTAT
Rubina Madni, JD, Office of Chief Counsel/Office of the Commissioner/FDA
Iftexhar Mahmood, PhD, GMB2/DCEPT/OTAT
Adamma Mba-Jonas, MD, PB/DE/OBE
Tao Pan, PhD, DBSQC/OCBQ
Tejashri Purohit-Sheth, MD, DCEPT/OTAT
Dorothy Scott, MD, PDB/DPPT/OTAT
Lisa Stockbridge, PhD, APLB/DCM/OCBQ
Maria Luisa Virata-Theimer, PhD, PDB/DPPT/OTAT
Yonggang Wang, PhD, PDB/DPPT/OTAT
Silvia Wanis, PharmD, BII/DMPQ/OCBQ
Steven Winitsky, MD, GMB1/DCEPT/OTAT

Boris Zaslavsky, PhD, TEB/DB/OBE
Pei Zhang, MD, PDB/DPPT/OTAT

ADMA Attendees:

James Mond, MD, PhD, Chief Medical Officer, Chief Scientific Officer, ADMA Biologics
Kaitlin Kestenberg, Senior Director, Compliance, Project Management, and Clinical Operations, ADMA Biologics
James Maloney, Senior Director, Regulatory Affairs, ADMA Biologics
Adam Pinkert, Vice President, Quality, Operations, ADMA Biologics
Adam S. Grossman, President and Chief Executive Officer, ADMA Biologics
Mike Druckman, Partner, Hogan Lovells LLP, Regulatory Counsel

Background and Objectives:

ADMA submitted a meeting request on February 11, 2019, to discuss the FDA directives included in the November 2, 2018, Information Request. The pre-meeting materials were submitted on February 11, 2019.

FDA provided its proposed responses to ADMA's questions on March 4, 2019. After reviewing the proposed responses, ADMA notified FDA on March 5, 2019, of its decision to proceed with the teleconference as planned.

Opening Remark from FDA:

FDA indicated at the outset that guidance and comments disseminated during this meeting are only preliminary and not binding in any way. FDA reiterated that the clinical data submitted in this BLA were to demonstrate efficacy in the treatment of PIDD patients using incidence of serious bacterial infections (SBI) as a primary endpoint. (b) (4) information has no relevance to this primary endpoint and is not clinically meaningful for the sought indication of PIDD. Thus, reference to (b) (4) information should be removed from the product labeling, product Certificate of Analysis (CoA) and specifications, and Lot Release Protocol template. This represents the Agency's current stance, which is consistent with its past communications regarding this issue.

Opening Remark from ADMA:

ADMA stated that they have no adversarial intent in insisting on including (b) (4) information in the product labeling and product specification without providing appropriate efficacy data. ADMA contended that the (b) (4) is fundamental to the constitution of the Immune Globulin Intravenous (IGIV) product as a distinct feature of the manufacturing process. ADMA contended that this feature of the product, therefore, merits some level of public disclosure.

General Discussion:

In response to ADMA's query regarding a path forward for an (b) (4) indication, FDA advised that the sponsor consider submitting a pre-IND meeting request in preparation for a new IND submission, along with supporting evidence from clinical efficacy data for an (b) (4) indication. FDA also acknowledged ADMA's proposed registry trial but declined to provide any feedback. FDA stated that, in order to make progress on this BLA,

ADMA would need to adequately address the labeling and remaining CMC issues, including those communicated in the recent Information Request via Prior-Approval Supplement (BL 125389/(b) (4)) for BIVIGAM.

FDA stated that the proposed clinical indication for ADMA's biologics license application, BLA 125590, is treatment of primary immunodeficiency disease (PID). The clinical data submitted in BLA 125590 are intended to demonstrate efficacy in treatment of PID using the incidence of serious bacterial infections of patients (SBI) as the primary endpoint. (b) (4) has no relevance to this primary endpoint.

FDA advised that intravenous immunoglobulin (IGIV) and subcutaneous immunoglobulin (IGSC) products contain antibodies against multiple infectious agents, as shown by in vitro and pharmacokinetic experiments. However, due to the absence of data showing that the antibody levels correlate with clinical efficacy or safety, FDA has not permitted the inclusion of this antibody information in product labeling. FDA advised that FDA approvals of IG products for specific infectious diseases, e.g., CMVIG, were based on clinical data showing reduced incidence of that infectious disease.

FDA encouraged ADMA to include (b) (4) data in the batch records because this information may be useful in the future if ADMA pursued the (b) (4) indication. ADMA should consider meeting with FDA for a pre-IND meeting if they wished to consider clinical studies to show safety and efficacy in (b) (4) patients.

Questions from ADMA Biologics, Inc. (ADMA):

Chemistry, Manufacturing, and Controls

ADMA Question 1:

In light of the information included in the meeting package, the response ADMA submitted to the Agency's IRs on November 6 and November 20, and all prior information and interactions between the Company and Agency staff, will the Agency withdraw its request to remove all references to (b) (4) from all documentation and meet with ADMA to initiate collaborative and constructive labeling negotiations?

If yes, we welcome a meeting with the Agency to further understand FDA's concerns and proposed solutions regarding these issues, in which case the Agency need not provide preliminary written answers to the questions below.

If not, then we respectfully request discussion and clarification of the following questions.

FDA Preliminary Response to Question 1:

No. As indicated in the FDA's prior interactions with your company, without relevant clinical data, references to (b) (4) should be removed from the product Certificate of Analysis, product release specifications, lot release protocol template, and product labeling.

Meeting Discussion:

There was no discussion of this question or comment during the meeting.

ADMA Question 2:

How should ADMA memorialize — in the Certificate of Analysis, product release specifications, lot release protocol, and lot release protocol template for ASCENIV™ — the specification, used while manufacturing the product during clinical trials, that each lot is tested for, and may only be released if it possesses, standardized levels of (b) (4)

FDA Preliminary Response to Question 2:

Please note that the comparability among the materials used in the clinical studies and later with the product manufactured at commercial scale is established by comparing a number of critical process and product parameters, and not on a particular measurement. Similarly, a product's manufacturing consistency is ensured by measuring several parameters, including those mandated by regulations for immunoglobulins. We do not recognize the (b) (4) in immunoglobulins as a critical parameter for ensuring manufacturing consistency and/or efficacy. We reiterate that your claim of criticality of (b) (4) in this product needs to be established in clinical and other relevant studies. Based on lack of relevant clinical data, we do not consider the (b) (4) to be relevant to the Certificate of Analysis, the product release specifications, the lot release protocol, and lot release protocol template for ASCENIV.

Meeting Discussion:

ADMA stated that there are two separate issues at hand: product manufacturing and product labeling. The applicant asked if it would be acceptable to FDA for the firm to retain (b) (4) information in the product specifications if they decide to remove any (b) (4) reference from the package insert.

FDA reiterated that there should be no mention of (b) (4) information in the product CoA and specifications and in the Lot Release Protocol template. It is, however, acceptable for the firm to include (b) (4) information in the manufacturing batch records for the firm's internal purposes only.

In response to ADMA's query, FDA stated that the firm should continue to make the product using their current manufacturing process (b) (4)

for internal purposes only. FDA advised that, should the BLA be approved, if ADMA decides to discontinue or change their manufacturing process, the firm will need to submit supporting data and information via prior approval supplements to report such proposed changes.

ADMA inquired how, if there is no mention of (b) (4) information in the product specifications, FDA would be able to verify the (b) (4) content of the product. In

response, FDA stated that the Agency would check the batch record during GMP inspection.

ADMA proposed to move the (b) (4) information from the Potency section to the Biological Activity section of the product CoA until they are ready to demonstrate efficacy for (b) (4) in ASCENIV and asked FDA if this would be acceptable to the Agency. FDA stated that this would not be acceptable.

ADMA Question 3:

How should ADMA memorialize — in the Certificate of Analysis, product release specifications, lot release protocol, and lot release protocol template for ASCENIV™ — the specification, used while manufacturing the product during clinical trials, that ASCENIV™ is required to be manufactured from (b) (4)

normal plasma source donors?

FDA Preliminary Response to Question 3:

Please see our Responses to Questions 1 and 2. In addition, for IGIV products, the only plasma information that is typically indicated on the Certificate of Analysis and the lot release protocol is whether the lot was manufactured from Source Plasma or Recovered Plasma.

Meeting Discussion:

There was no discussion of this question or comment during the meeting.

ADMA Question 4:

How should ADMA fulfill its regulatory obligation to employ identity testing capable of differentiating by chemical, physical, or immunological means ASCENIV™ from BIVIGAM® since both are now manufactured by ADMA in the same plant?

FDA Preliminary Response to Question 4:

Please note that the identity testing requirement of IGIV products has evolved in recent years to a less burdensome approach of confirming that the final packaged product is made from human IgG. ADMA's original proposal to use (b) (4) (SOP QC2049) in the identity testing of ASCENIV manufactured in the same plant as BIVIGAM appears to be sufficient.

Meeting Discussion:

ADMA inquired how the firm is supposed to properly differentiate ASCENIV from other products manufactured in the same facility by testing of IgG solely by (b) (4) without using an identity test in compliance with 21 CFR 610.14. FDA explained that in hospitals and pharmacy practice, the specific brand of IGIV product is not identified; therefore, there appears to be no need to differentiate ASCENIV from BIVIGAM. Furthermore, the products are manufactured in the same way and have the same clinical indication.

In addition, under GMP conditions, incoming raw materials and each product lot must be tracked via manufacturing records; if not, the manufacturing process would not be GMP-compliant. ASCENIV and BIVIGAM are of the (b) (4) concentration, (b) (4) for the PIDD indication. These products may be substituted for one another in clinical practice because the only difference between the two is (b) (4). The applicant, however, still needs to differentiate ASCENIV and BIVIGAM from Nabi-HB, which is a hyperimmune IgG made in the same manufacturing plant.

In response to ADMA's query, FDA clarified that the term "interchangeable" in the context of this discussion was not being used to invoke a discussion about the 351(k) biosimilar application pathway.

ADMA asked if FDA would consider the PK data to be clinically relevant to distinguish ASCENIV from BIVIGAM. FDA stated that such PK data would have utility from clinical perspective only if there are any efficacy data in support of the (b) (4) indication. The applicant asked if these PK data are useful for any other purposes, such as for demonstration of biological activity of the IGIV product, if they have no clinical relevance.

In response, FDA asked whether ADMA has shown any significant difference in half-life or other biological characteristics of ASCENIV. ADMA explained that the pathogens selected for the PK study are pathogens that specifically infect PIDD patients and are relevant to the patients studied in the clinical trial. ADMA stated that their PK studies have demonstrated that the half-lives of antibodies against different pathogens are different for ASCENIV and other IGIV products.

ADMA stated that the firm was asked by FDA to provide additional drug interaction data that might merit a need to be included in the package insert. FDA stated that the Agency is aware of those data, but the data are not supportive of clinical efficacy and should not be used or mentioned in the labeling. FDA stated that there is no clear correlation between those data and clinical outcomes.

FDA requested that the firm consider submitting a version of the master batch record form for review sooner rather than later. ADMA asked the Agency for specific feedback as to which part of the batch record should include (b) (4) information. FDA deferred that to the firm's discretion. FDA also stated that there are still other open CR issues that need to be resolved prior to approval.

ADMA asked whether, if the firm agrees to comply with FDA's request regarding (b) (4) references, FDA anticipates any additional bottlenecks that would delay the approval of this BLA. FDA stated that it would be contingent upon how swiftly ADMA makes such decision as there is not much time remaining in this BLA review cycle. FDA further stated that review is still ongoing, and the Agency is unable to provide feedback regarding the final regulatory action.

ADMA asked, should ASCENIV be approved for the PIDD indication, whether it would be possible to provide efficacy data in support of a new indication for (b) (4) infection, in addition to the existing PIDD indication, in the product labeling post-BLA approval without repeating clinical studies in support of the PIDD indication. FDA stated that this would be possible. However, as stated above, it would require adequate clinical data showing efficacy in (b) (4) infections.

ADMA asked if the FDA positions expressed during this meeting represent the Office opinion. FDA stated that this question would be addressed in the meeting minutes. However, FDA stated that the Agency is interested in knowing what the firm's plan is and in working with the applicant to determine the best regulatory path forward.

Labeling

Regarding Questions 5 to 8:

We are unaware of clinically meaningful data to support the inclusion of (b) (4) information in your product labeling. Under the regulatory standards set forth in 21 CFR 201.57(c)(8), theoretical safety concerns, such as those related to levels of (b) (4) in ASCENIV, do not belong in product labeling.

Meeting Discussion:

There was no discussion of these questions or comments during the meeting.

ADMA Question 5:

How should ADMA disclose to prescribers in labeling the factual information that ASCENIV™ contains (b) (4)

FDA Preliminary Response to Question 5:

This information is not based on clinical data and is not appropriate for the labeling.

Please see our comments above (under "Labeling").

Meeting Discussion:

There was no discussion of this question or comment during the meeting.

ADMA Question 6:

If the Agency is concerned about implied efficacy claims as it has stated in the past, what language in the labeling will be sufficient to eliminate those concerns?

FDA Preliminary Response to Question 6:

Please see our Responses to Questions 1, 2, and 5. We reiterate that, in the absence of adequate clinical data to support such a reference, mention of (b) (4) is not appropriate for the labeling.

Please see our comments above (under “Labeling”).

Meeting Discussion:

There was no discussion of this question or comment during the meeting.

ADMA Question 7:

How should ADMA disclose to prescribers appropriate warnings, precautions, and information in labeling regarding the risk of interference between ASCENIV™ and (b) (4) therapeutics or diagnostics which may pose serious safety concerns?

FDA Preliminary Response to Question 7:

Under 21 CFR 201.57(c)(8), the Drug Interactions section of the prescribing information “must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs ...” No mention of risk of interference between ASCENIV and (b) (4) therapeutics or diagnostics should be made in the labeling, because there are no adequate clinical data meeting the regulatory standard set forth in 21 CFR 201.57(c)(8) to support such a reference.

Meeting Discussion:

There was no discussion of this question or comment during the meeting.

ADMA Question 8:

How should ADMA convey to prescribers in labeling the results of pharmacokinetic testing that measured subjects’ levels of antibodies to selected pathogens, including (b) (4)

FDA Preliminary Response to Question 8:

Mention of the pharmacokinetic testing results that measured subjects’ levels of antibodies to selected pathogens, including (b) (4) is not appropriate for the product labeling.

Please see above under “General Comment.”

Meeting Discussion:

There was no discussion of this question or comment during the meeting.

Post-Meeting Comment:

Regarding the above discussion, the Office of Tissues and Advanced Therapies agrees that there should be no mention of (b) (4) information in the product CoA and specifications and in the Lot Release Protocol template. It is, however, acceptable for ADMA to include (b) (4) information in the manufacturing batch records for the firm’s internal purposes only.