



Official Meeting Summary

Meeting ID #: CRMTS #8012 and NDA BN090067
Product name: Isoplate Solution
Sponsor: B. Braun Medical
Meeting type: Type A
Meeting category: NDA
Meeting date & time: June 30, 2011, 9:30 a.m. – 10:30 a.m.
Meeting format: Teleconference
Meeting Leader: Basil Golding, M.D.
Meeting Recorder: Iliana Valencia and Mike Yoler

FDA Attendees:

Basil Golding, M.D., Director, OBRR/DH
Jaro Vostal, M.D., Ph.D., Branch Chief, OBRR/DH/LCH
Jan Simak, Ph.D., Visiting Scientist, OBRR/DH/LCH
Chinying Wang, Ph.D., Mathematical Statistician, OBE
Yolanda Branch, Ph.D., Pharmacologist, OBRR/DH
Lore Fields, MT (ASCP) SBB, Consumer Safety Officer, OBRR/DBA/BPB
Dana Jones, Consumer Safety Officer, OCBQ/DCM/APLB
Lisa L. Stockbridge, Ph.D., Branch Chief, OCBQ/DCM/APLB
Mike Yoler, B.S., Consumer Safety Technician, OBRR/DBA/RPMB
Iliana Valencia, M.S., Regulatory Project Manager, OBRR/DBA/RPMB

B. Braun Medical Inc. Attendees:

Rebecca Stolarick, Director, Regulatory Affairs
Patti Smith, Manager, Regulatory Affairs
Christina Hahn-Major, Regulatory Affairs Specialist, Regulatory Affairs
Kathy Holdren, Labeling Specialist, Regulatory Affairs
Elaine Ogunbiyi, Associate Director, Regulatory Affairs Operations

Affiliate Attendees: CaridianBCT

Mark Holmes, VP, Regulatory & Government Affairs
Isabel McGann, Sr. Regulatory Affairs Specialist
Anna Razatos, Therapy Scientist
Carolyn Braithwaite, Laboratory Supervisor
Bob Schuyler, Director Clinical and Scientific Affairs

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Background and Objectives:

B. Braun Medical Inc. submitted a meeting request on May 9, 2011, which included the pre-meeting material. B. Braun's stated purpose of the meeting was to discuss the complete response letter dated February 2, 2011.

On June 28, 2011, FDA provided B. Braun with preliminary responses. After reviewing the responses, the sponsor notified FDA on June 29, 2011 of their decision to proceed with the meeting as planned.

Following introductions, B. Braun thanked FDA for reviewing the information and participating in the meeting and indicated they had only a few items for clarification.

Clinical Questions

Protocol II: In Vitro Platelet Quality Study:

Sponsor Question 1:

Related to comment #2 (P-selectin): The Protocol II in vitro study met its primary endpoint of pH > 6.2, but failed in one secondary endpoint: the surface P-selectin expression, which is more than 20% higher in the test group (22±15.4 %) compared to the control group (15.1±9.1 %). FDA is concerned regarding high P-selectin expression (> 20% higher compared to control) on five day Isoplate stored platelets. This finding could have clinical consequences. Please comment.

CaridianBCT acknowledges that there is a difference in p-selectin surface expression between Test (Isoplate-stored platelets) and Control (plasma-stored platelets). P-selectin failed to meet the acceptance criteria that the difference between Test and Control is less than 20% with a 95% confidence interval. However, as discussed with FDA in the pre-NDA meeting on September 9, 2009 (CRMTS #7147) the levels detected for Isoplate-stored platelets in Protocol II are consistent with commonly transfused products.

The p-selectin surface expression is an indicator of platelet activation¹. However there is no consensus in the literature that p-selectin correlates to clinical outcomes. Both Michelson² and Berger³ demonstrated in animal models that p-selectin does not mediate platelet clearance and hence does not affect platelet circulation in vivo. Michelson² and Krishnamurti⁴ reported that thrombin activated platelets lose surface p-selectin upon transfusion, and those platelets continue to circulate and function in animal models. Michelson² and Krishnamurti⁴ concluded that these platelets are just as effective as fresh platelets at decreasing blood loss. In summary these studies suggest the measurement of p-selectin surface expression in stored platelet products "should not be used as a predictor" of in vivo function¹.

CaridianBCT does not agree with FDA that p-selectin levels measured for Isoplate-stored platelets will have clinical consequences. Nevertheless, CaridianBCT and B. Braun Inc. do agree to a postmarket surveillance study for Isoplate-stored platelets

(500 transfusions in 18 months) as was discussed with the Agency in the pre-NDA meeting on September 9, 2009 (CRMTS #7147). Is this acceptable to the FDA?

FDA Response to Question 1:

No, your proposal of the postmarket surveillance study for Isoplate stored platelets with sample size of 500 transfusions in 18 months is not acceptable. Platelet additive solutions are a new type of product with very limited clinical experience in the United States. In addition, FDA is concerned regarding the failed secondary endpoint of your *In vitro* study - high P-selectin expression (> 20% higher compared to control) on five day Isoplate stored platelets. Please note that it is premature to discuss an option of a postmarket surveillance study before complete results of NDA studies including Protocol III are reviewed by FDA.

Discussion:

CaridianBCT acknowledge there is a difference between test and control in the p-selectin surface expression. They propose to address this issue by adding the p-selectin data to the secondary endpoints in the labeling to be consistent with competitors' labeling. FDA is still evaluating the product and will need to see all the data from the radiolabeling study before a conclusion can be reached. CaridianBCT is in the process of repeating the *in vivo* test that FDA requested and is still waiting for the results of the radiolabeling study. When the study is completed, Caridian will provide the information to FDA.

Protocol III: In vivo Platelet Study:

Sponsor Question 2:

Related to comment #4: FDA has a serious concern about your results from the Protocol III In Vivo Platelet Study. In the paragraph 5.3.5.1.16.2.1 Discontinued Subjects, you stated that fifteen subjects from the Yale site were excluded from analysis in Protocol III: In Vivo Platelet Study. For II evaluated subjects at the Yale clinical site 28 subjects were enrolled, two of them did not meet the inclusion criteria and 15 subjects were excluded from evaluation for various reasons. The "low day 5 pH for test platelets" - (b)(6)-- should be regarded as a product failure. The frequency of exclusion such as "radiolabel anomalies" -----(b)(6)-----, or "isotope not received" (b)(6), were much higher than those seen in comparable studies. In contrast, there was no subject exclusion from analysis at the Dartmouth clinical site, which reported only three volunteer screening failures. The marked difference in exclusion rates between Yale and Dartmouth clinical sites demonstrates that the study quality was not equivalent at these two sites. The exclusion of 15 subjects at the Yale site may represent a bias in a statistical evaluation of results. Please provide additional data on a group of 12 donors evaluated with the In Vivo Platelet Study with the same design as in the Protocol III and performed at a third independent clinical site.

Per FDA's request, an additional N=12 in vivo data points will be collected at a third independent study site. Protocol III was amended (IND 13684/0032) February 28, 2011 to increase enrollment and add the Hoxworth Blood Center as the third independent clinical trial site. Due to FDA's concern regarding the Yale data, we will exclude the

Yale data from analysis and combine the new data acquired from Hoxworth with Dartmouth in the final analysis. This was amended and submitted on April 1, 2011. Is this acceptable to FDA?

FDA Response to Question 2:

FDA can not comment on acceptability of data which have not been submitted for review yet. Please submit results of *In Vivo* Platelet Study (Protocol III) performed at the third independent clinical site - the Hoxworth Blood Center or provide an update on the status of this study.

Discussion:

B. Braun Medical is satisfied with FDA's response to question 2.

Clinical Pharmacology Questions:

Sponsor Question 3:

Related to comment #7a: It is noted that B. Braun Medical Inc. conducted the chemical, biological and physical functional testing on the Excel® plastic container in accordance with the USP requirements and additional B. Braun tests. The product's proposed indication is for platelet storage in the following ratio: 65% Isoplate solution and 35% plasma. It is stated in the label that Isoplate solution will not be used for direct infusion. However, please note Isoplate will be directly infused into patients as a combination product (Isoplate and plasma); this is of concern because there can be an accumulation of extractables/leachables beyond the acceptable range with multiple use (doses) of product. The levels of each extractable/leachable need to be assessed at the maximum daily dose of the combination product to ensure that these are within an acceptable range. Please see the comments below:

a. Please note the toxicological evaluation of extractables/leachables from the plastic should be based on animal studies that defined a toxic dose of an IV administered compound and on the anticipated clinical application of the product. Please identify each extractable/leachable and calculate their levels at the maximum clinical dose, to ensure that it is within an acceptable range.

*B. Braun & CaridianBCT have consulted with a toxicologist from -----(b)(4)-----
----- to provide a report related to the extractable/leachables that may be found in the final blood product (hyperconcentrated platelets stored in 65% Isoplate in CaridianBCT's Extended Life Platelet bag). This report is enclosed in this submission. Please refer to Table 6 of the report below. Does this report address FDA's concerns?*

[b(4)]

b. Please electronically submit all preclinical (toxicological) studies that are cross referenced in order to complete the file.

B. Braun & CaridianBCT will not be cross referencing preclinical (toxicological) studies. All relevant biological information on the extractable/leachable in the final product is referenced in the B. Braun DMFs referenced in our application (DMF #'s: -----(b)(4)-----

c. Please keep labeling (overdose, warnings, precautions, and contraindications) consistent with the FDA approved product Isolyte.

Please refer to question #4.

FDA Response to Question 3:

Yes, the information submitted appears to address our concerns. However all data will be considered upon submission to determine the adequacy of the program.

Discussion:

When FDA refers to “program” they refer to the totality of the submission.

Sponsor Question 4:

Related to comment #7c and #13: Contraindications: The labeling for the drug approved in CDER under the ANDA has several warnings on usage with certain patient populations. Please clarify why those warnings have not been included in this package insert or supply studies that have changed the warnings.

B. Braun would like to discuss with FDA the request to include cautions/warnings and contraindications related to Isolyte S, as a ----(b)(4)-----, in the Isoplate, for use as a platelet additive solution (PAS). The information is not relevant for use as a PAS. It is not known if those cautions and warnings apply, as there was no data collected under the clinical trials to support the statements. B. Braun proposes that if any new information results from the trials or post market surveillance study that these new cautions/warnings be added at that time to the Isoplate labeling, as a CBE-30. Is this acceptable?

FDA Response to Question 4:

Please include in the labeling precautions/ warnings related to overdosing of the following components: Potassium, Magnesium, and Gluconate. FDA may request additional precautions/warnings or other changes in labeling pending results of your studies.

Discussion:

B. Braun would like the labeling to state that the solution contains potassium, magnesium and gluconate. In addition they propose including a generic statement in labeling similar to, “there is a risk for toxicity due to potassium, magnesium and glutamate from multiple transfusions.” It is acceptable to the FDA that the sponsor provides a general overdose/toxicity statement but B. Braun should include any information related to overdose or toxicity and how it will be monitored in patients.

Sponsor Question 5:

Caridian BCT notes that FDA did not comment on the bacterial testing provided in Module 5.3.5.4, is this data sufficient to address any concerns related to bacterial testing of the platelet products?

FDA Response to Question 5:

Results from your study on the bacterial testing provided in Module 5.3.5.4 demonstrated that bacterial growth in platelets stored in Isolyte S versus plasma is species specific. You stated that for (b)(4) of the (b)(4) strains evaluated in this study -----(b)(4)-----, there were no outstanding differences in bacterial growth between Isolyte S and plasma; for (b)(4)- of the (b)(4) strains evaluated in this study -----(b)(4)----- growth was faster in Isolyte S in comparison to plasma; for (b)(4) of the (b)(4) strains evaluated in this study -----(b)(4)----- growth was slower in Isolyte S in comparison to plasma. Your conclusion that Isolyte S as a platelet storage medium does not increase the overall risk of bacterial growth or bacterial reactions due to contaminated platelet products in comparison to the current plasma-stored platelet products is acceptable.

Discussion:

B. Braun Medical is satisfied with FDA’s response to question 5.

Decisions made and/or agreements reached:

None.

Issues requiring further discussion:

None.

Action items for Cerus:

1. B. Braun will respond to the CR letter towards the end of October or beginning of November of 2011.

Attachments/Handouts:

None.

END