

Meeting Response Memo, June 28, 2011 - Isoplate Solution

DEPARTMENT OF HEALTH & HUMAN SERVICES
Service

Public Health

Food and
Drug Administration

1401 Rockville Pike

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Meeting Response Memorandum

Our Reference: CRMTS #8012
Ref. # BN090067

Division of Blood Applications

TODAY'S DATE: June 28, 2011

PAGES: # 5

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SUBJECT: Summary of FDA Internal Meeting

PRODUCT:

We completed our review of your information package for Isoplate Solution and are providing the following responses to the questions you posed in the package. Although we continue to reserve June 30, 2011 at 9:30 am EST for a teleconference with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us as soon as possible so that we may clear the meeting time. Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time.

THANK YOU

Questions from the Sponsor:

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.

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.

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)

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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.

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.

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)----- strains evaluated in this study (-----b(4)-----), there were no outstanding differences in bacterial growth between Isolyte S and plasma; for –b(4)----- strains evaluated in this study (--b(4)-----) growth was faster in Isolyte S in comparison to plasma; for –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.