



January 4, 2006

In regards to: Attachment #10 submitted with BloodSource comments for FR DOC. 05-19727 (Reference# 2005-D-0330/C11)

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Dear Jenny Butler,

Per our conversation, we have confirmed with Larry Dumont, of Gambro BCT, that we may share with the FDA all of the pre- and post-plateletpheresis data that was provided in Attachment #10. If you have additional questions, please do not hesitate to contact me at your convenience.

Respectfully,

Patricia C. Grace, RN  
Director of Operations - Quality/Regulatory  
BloodSource

**Preliminary Data:**

A series of 409 Trima version 4 and 79 Trima Accel procedures were evaluated for the prediction accuracy of the post platelet count algorithm. The study is described in Transfusion 2004;44(S):9A (McAteer and Langely).

In another series, pre-donation (Cpre) and post-donation (Cpost measured) peripheral venous platelet concentrations were determined in 887 Trima Accel collections in three different blood centers. Based on apheresis run parameters and donor characteristics, the predicted donor post platelet concentration was calculated (Cpost calculated) using the Trima algorithm. These data are summarized in Table 1. The determination of post donation platelet concentrations and assessment of prediction accuracy was a secondary outcome of these studies. Because the Cpre was not always available prior to the procedure, these had to be incorporated post facto into the analysis. Minimum post procedure Cpost calculated (i.e., the predicted post donation donor platelet count) was set to less than 100,000 platelets/ $\mu$ L for some of the Site 2 collections, in conformance with Trima Accel labeling and medical director decisions at the center.

**Table 1: Summary of 887 donations with pre and post donor venous platelet counts (1000 platelets/uL)**

Center	Variable	N	Mean	Std Dev	Minimum	Maximum
Site 1	Cpre	158	247	48	164	442
	Cpost calculated	158	162	33	106	267
	Cpost measured	158	204	42	140	381
Site 2	Cpre	320	252	62	123	755
	Cpost calculated	320	117	48	39	569
	Cpost measured	320	181	47	107	578
Site 3	Cpre	258	270	65	179	630
	Cpost calculated	409	159	45	99	416
	Cpost measured	409	201	45	112	427

These data were used to assess the accuracy of the Trima algorithm using a general linear model (PROC GLM; SAS v. 9.1, Cary, NC). As seen in Figure 1, the Trima algorithm makes a conservative estimate of donor post platelet counts (PLT post calculated) compared to the measured donor post procedure platelet count (PLT post measured). For example, at a Trima algorithm calculated post donation donor platelet count of 100,000 platelets/ $\mu$ L, the estimated measured value is 158,000 platelets/ $\mu$ L; with 95% predicted to be greater than 118,000 platelets/uL (lower 95% prediction of the regression). Furthermore, with a Trima predicted post platelet count of 78,000 platelets/ $\mu$ L, 95% of procedures are expected to be above 100,000 platelets/uL. (cf. Table 2)

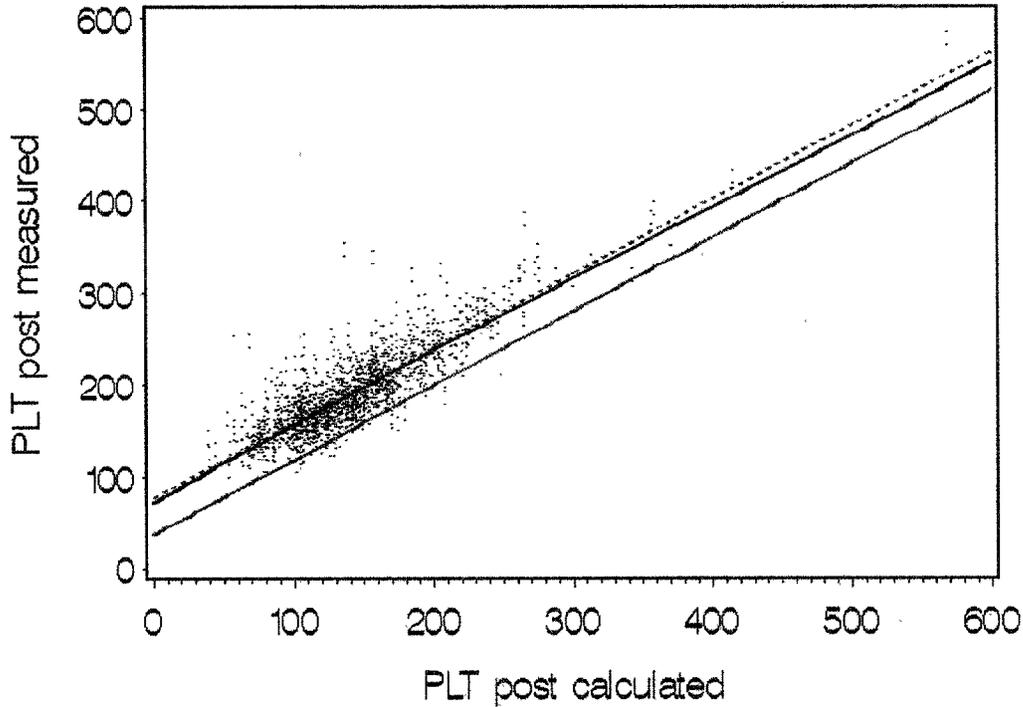
From these data, we conclude that the Trima algorithm provides a substantial margin in predicting the donor post apheresis platelet count; probably due to platelet mobilization from the spleen, which is not accounted for in the Trima algorithm. Setting the minimum acceptable Trima calculated post donation platelet count at 50,000 platelets/ $\mu$ L (the minimum allowed by cleared labeling in the Trima operator's manual), it is anticipated that 95% of procedures at this extreme will have a donor post count greater than 77,000 platelets/ $\mu$ L.

**Figure 1:** Multiple regression with best estimate (dotted red), lower 95% CI on best estimate

(black), and the lower 95% prediction limit (solid red). Platelet counts are shown as thousand per microliter. N=887

$$PLT \text{ post measured} = 77.1 + 0.81 * (PLT \text{ post calculated})$$

Prediction



**Table 2: Relationship of Trima Calculated Post Platelet Count, the Regression Estimate for Measured Post Platelet Count, and the Lower 95% Confidence Interval for Measured Post Platelet Count. (1000 platelets per uL)**

Trima Calculated	Regression Estimate	Lower 95% Prediction Limit
39	109	69
41	110	70
46	114	73
50	118	77
54	121	81
55	122	82
59	125	84
60	126	85
64	129	89
71	135	94
78	140	100
100	158	118

## RISK ANALYSIS

The only specific risks to study subjects are those associated with small volume peripheral venous blood sampling; hematoma, infection at the venipuncture site, and vasovagal reactions which could result in lightheadedness, nausea and fainting. Simple venipuncture has been judged by FDA as a non-invasive procedure (21 CFR 812.3(k)).

The platelet apheresis collection procedure is not part of the investigational procedure contained in this proposal. The apheresis donation is completed using a 510(k) cleared device, the Trima Apheresis System, that is used in accordance with the FDA reviewed indications and instructions for use; thus exempted from 21 CFR 812. For background however, we believe the reviewers will be interested in the risks associated with apheresis and a discussion of nadir platelet counts following platelet collection by apheresis.

The risks to the subjects during the prestudy platelet apheresis donation are those inherent to apheresis systems in general during a typical donation. These include the risk of hematoma, over delivery of anticoagulant, toxicity or non-sterility of the disposable set, the risk of clots, particulates or air being returned to donor, hypovolemia, blood trauma (hemolysis, activation of coagulation or complement systems, or platelet activation), and equipment issues including loss of power, general electrical safety, and centrifuge safety. The blood is anticoagulated with citrate anticoagulant. Some donors will experience tingling around the mouth and nose that will rapidly resolve by slowing the procedure, stopping the procedure, or administering oral calcium supplements. These symptoms can very rarely progress to seizures, tetany, or death if not reported by the donor and proper care given by the operator. All of these risks have been assessed by Gambro BCT and found to be minimal when using the Trima system.

The risks to the subjects by lowering their circulating platelet count as a consequence of the prestudy apheresis platelet donation is not changed from the attendant risks associated with the use of the Trima apheresis system according to the 510(k) cleared manufacturer's instructions for use. The Trima algorithm for estimating by calculation the platelet donor's post procedure platelet count provides a large margin for donor protection since it does not consider splenic platelet mobilization to the peripheral circulation as discussed in the preliminary data. This is significantly more conservative than other algorithm approaches that include mobilization factors. The latter would be expected to provide a more accurate prediction of the post count but, with the large uncertainty of these models, would provide a lower 95% prediction limit well below the calculated estimate. For example, an algorithm which adjusts for platelet mobilization may estimate a post platelet count of 100,000 platelets/ $\mu$ L, but the lower 95% prediction limit for this estimate could be 60,000 platelets/ $\mu$ L. In contrast, the Trima algorithm, which might calculate an expected post count of 100,000 platelets/ $\mu$ L, will in fact, provide a lower 95% prediction limit at 118,000 platelets/ $\mu$ L as seen in our preliminary data (Table 2). Likewise, a Trima algorithm calculation of a 50,000 platelets/ $\mu$ L post platelet count will provide a lower 95% prediction limit of 77,000 platelets/ $\mu$ L. Thus, the Trima algorithm has a built-in safety margin against over depletion of platelets from the apheresis donor.

The risk to healthy donors leaving an apheresis setting with 100,000 platelets/ $\mu$ L or less has not been reported in the literature. In a study that may best represent a clinical setting with normal endothelium and a non-consumptive thrombocytopenia, Slichter and Harker assessed fecal

blood loss in 20 stable aplastic thrombocytopenic patients.<sup>1</sup> They observed no increase in stool blood loss when subject platelet counts were above 10,000 platelets/ $\mu$ L as compared to normal subjects. These same investigators examined the bleeding time response as a function of platelet counts in aplastic thrombocytopenic patients. For platelet counts greater than 100,000 platelets/ $\mu$ L, the template bleeding time was  $4.5 \pm 1.5$  minutes. Their data showed an average bleeding time of 10.5 minutes with a platelet count of 77,000 platelets/ $\mu$ L. This can be compared to template bleeding times following ingestion of aspirin (ASA). Cahill and coworkers administered placebo, 75mg ASA, or 300mg ASA to healthy volunteers for 14 days. Twenty-four hours following the last dose, mean template bleeding times were 6.4, 9.5 and 11.1 minutes, respectively.<sup>2</sup> Sonksen et al. made similar observations of the median template bleeding time two hours following the last dose of a 7-day course of placebo, 75mg ASA, or 300mg ASA: 3 minutes, 7 minutes, and 6.4 minutes, respectively.<sup>3</sup> This evidence suggests an increase in template bleeding times for a platelet count of 77,000 is approximately what would be expected after dosing with one aspirin.

In an in-hospital patient series, Lawrence et al. assessed minor bleeding as a function of morning platelet counts.<sup>4</sup> While not specifically analyzed by the authors, there appears to be no significant increase in minor bleeding (e.g.: petechiae, cutaneous bleeding, oral bleeding, epistaxis) risk in this patient series until the morning platelet count drops below 50,000 platelets/ $\mu$ L.

In the setting of hypoproliferative thrombocytopenia typically induced by therapeutic cancer treatment regimes, the prophylactic transfusion trigger is generally set at 10,000 to 20,000 platelets/ $\mu$ L based on the clinical picture, and in some settings driven strictly as a therapeutic intervention based on clinical observations of bleeding.<sup>5</sup>

The risk to healthy donors leaving an apheresis setting with platelet counts of 50,000 to 100,000 has not been reported. The evidence presented above suggests a post procedure platelet count of 77,000 would not have a significant effect on the donor risk. We are not aware of any reports of donor bleeding episodes or related complications following donation of platelets by apheresis.

Therefore, we conclude there is no significant risk to the platelet apheresis donor due to the reduction of circulating platelet count when the apheresis device is used according to the manufacturer's directions for use. Again, the only risks specifically related to the proposed study are those related to the simple venipuncture and withdrawal of small volumes of blood for complete blood count (CBC).

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<sup>1</sup> Slichter SJ, Harker LA. Thrombocytopenia: Mechanisms and management of defects in platelet production. *Clin Haematol* 1978;7:523-539.

<sup>2</sup> Cahill RA, McGreal GT, Crowe BH, et al. Duration of Increased Bleeding Tendency after Cessation of Aspirin Therapy. *J Am Coll Surg* 2005;200:564-573.

<sup>3</sup> Sonksen JR, Kong KL, Holder R. Magnitude and time course of impaired primary haemostasis after stopping chronic low and medium dose aspirin in healthy volunteers. *Br J Anaesth* 1999;82:360-5.

<sup>4</sup> Lawrence JB, Yomtovian RA, Dillman C, et al. Reliability of automated platelet counts: comparison with manual method and utility for prediction of clinical bleeding. *Am J Hematol* 1995;48:244-250.

<sup>5</sup> Slichter SJ. Relationship Between Platelet Count and Bleeding Risk in Thrombocytopenic Patients. *Transfusion Medicine Reviews* 2004;18(3):153-167.

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## Modified MPT Workflow Process Validation

### Discussion

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Six months of platelet testing was examined to determine the reliability of using parent bag testing to divide triple platelet products without falling below the  $3.0 \times 10^{11}$  platelet yields specified for these products. 528 intended triple products were examined for the six month period February 2004 – August 2004. In two instances, a platelet with a sufficient platelet count to be split into a triple product ( $9.3 \times 10^{11}$ ) was found to have an insufficient platelet in the progeny products. In both of these instances the platelet testing was performed using the Baker 2991 Hematology Analyzer. These instruments required a manual dilution step for platelet concentrates. This step contributed to analytical variability on the Baker analyzers. With the implementation of the ABX Pentra XL 80 analyzers on 6/1/04 the precision of platelet concentrate testing improved. This change will add to the reliability of parent bag testing.

Examination of six months of platelet testing results for triple platelet products indicates that a cutoff of  $9.3 \times 10^{11}$  will provide a high degree of assurance that platelet products contain at least  $3.0 \times 10^{11}$  platelets (a 99.6% reliability rate). During performance of the ABX Pentra XL 80 validations, it was found that the coefficient of variation (C.V.) for platelet testing (using platelet-rich plasma) was 1.41% and 0.83% for the analyzers, respectively (S.N. 306PXL0591 & S.N. 309PXL0735). This level of precision is consistent (or better) than the 99.6% reliability found through record review. The performance of the ABX Pentra XL 80 analyzers will reliably yield platelet products meeting the  $3.0 \times 10^{11}$  platelet yield specifications using a  $9.3 \times 10^{11}$  cutoff.

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## Modified MPT Workflow Process Validation

### Discussion

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Forty data point were examined for intended double platelet products. Of the forty intended double platelet products, twenty eight products (70%) had platelet counts between  $6.3 \times 10^{11}$  –  $9.2 \times 10^{11}$ . Five of the intended double platelet products (12%) had a platelet count in excess of  $9.2 \times 10^{11}$  (threshold for triple platelet products). Seven intended double platelet products (18%) yielded single platelet products. In no instance would the use of parent bag testing have resulted in a platelet product being released with a substandard platelet dose ( $< 3.0 \times 10^{11}$ ). Correlation between parent bag results and progeny bag results was generally very good. In the forty collections examined there was a slight bias (2%) toward higher yields in the progeny counts. This bias will tend to promote higher yield platelet products and prevent the inadvertent production of low yield products.

Examination of double platelet collections confirms that a cutoff of  $6.3 \times 10^{11}$  will provide a high degree of assurance that platelet products will contain at least  $3.0 \times 10^{11}$  platelets.

# Double Platelet Correlation Study

