

Statistical Final Memo, June 2, 2012 - SOLX® System

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Division of Biostatistics (HFM-215)

Statistical Review and Evaluation

Type/Application ID/Amendment #: NDA/BN 110059

Subject: HEMERUS LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive

Applicant: Hemerus Medical, LLC

Indications for Use:

- Pre-storage leukocyte reduction of CPD whole blood followed by preparation of SOLX® Red Blood Cells, Leukocytes Reduced prepared at ambient temperature and placed at 1 to 6° C within (b)(4) hours of collection. SOLX® Red Blood Cells, Leukocytes Reduced may be stored at 1 to 6° C for up to 42 days after collection.
- Preparation of Fresh Frozen Plasma (FFP), Leukocytes Reduced prepared and frozen at -18° C or below within 8 hours of collection. Fresh Frozen Plasma (FFP), Leukocytes Reduced may be stored at -18° C or below for up to one year after collection.

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Primary Statistical Reviewer: Chinying Wang, Ph. D. (HFM-219)

Supervisory Concurrence:

1st Level Review

Supervisor Name: Tie-Hua Ng, Ph. D.

Supervisor Title: Team Leader, OBE/DB/TEB

Concur _____ Not Concur _____

Supervisory Signature

2nd Level Review

Supervisor Name: Boguang Zhen, Ph.D.

Supervisor Title: Branch Chief, OBE/DB/TEB

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HFM- 215 /Chronological File (OBE/DB)

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The study was conducted according to protocol PC387580, “*In Vitro* and *In Vivo* Evaluation of Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive”. Based on the reported results, the clinical study showed that the primary endpoints of RBC mass recovery, leukoreduction efficiency, hemolysis at end of storage, and 24-hour radiolabeled recovery were met for all **SOLX®RBC** processing groups. In addition to the assessment of the primary endpoints, this statistical reviewer performed a comparative analysis to investigate the effect of hold time at room temperature on labile coagulation factors such as Protein S, Factors V, Factor VIII and Factor XI. -----

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The study was conducted according to protocol PC387580, “*In Vitro* and *In Vivo* Evaluation of Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive”. In the United States liquid red blood cell (RBC) storage systems are currently licensed by the FDA for up to six weeks of refrigerated (1-6°C) storage. Improved systems with longer storage periods are desired to reduce the losses that occur from outdating, to enhance the quality and survival of routinely stored RBC's, to meet the needs of remote locations and to extend the usefulness of autologous donation.

The study required a total of 240 subjects completing study requirements; 180 test subjects and 60 control subjects. Fifty-six of the 180 total test subjects were evaluated for autologous, radiolabeled, in vivo red cell recovery and red cell survival. The remaining test subjects, and all control subjects, donated a unit of whole blood for in vitro evaluation only.

Three processing groups of 60 whole blood units each were studied using the SOLX® System. Sixty units of control whole blood units were also tested under the processing conditions of Group 2. Processing groups are summarized below:

- Group 1: Up to two hour room temperature hold prior to whole blood filtration and processing at room temperature (60 test units). RBCs refrigerated and plasma frozen within 8 hours.
- Group 2: Greater than six hour room temperature hold prior to whole blood filtration and processing at room temperature within eight hours (60 test and 60 control units). RBCs refrigerated and plasma frozen within 8 hours.

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Each of three processing groups will consist of 60 test units completing the study. One control group will consist of 60 units completing the study processed according to Group 2 conditions. The allocation of sample size for each group is shown below.

Sample Sizes by Processing Group

G 1 Group 2 Group 3Units

	Group 1		Group 2			(b)(4)	
	Test Units		Test Units		Control Units	---(b)(4)----	
	In Vitro Only	In Vivo & In Vitro	In Vitro Only	In Vivo & In Vitro	In Vitro Only	-(b)(4)- - (b)(4)-	-(b)(4)- - (b)(4)-
Number of Units	46	14	46	14	60	(b)(4)	(b)(4)
Total	60		60		60	(b)(4)	

Primary Endpoints

Primary study endpoints of RBC mass recovery, leukoreduction efficiency, hemolysis at end of storage and 24-hour radiolabeled recovery were evaluated using predetermined confidence and reliability limits for binomial attribute testing. The objective performance criteria for evaluation of RBC endpoint analysis included:

- A one-sided 95% lower confidence limit for the true proportion of units with a filtration recovery of red blood cell mass of at least 85% is greater than 95%.
- A one-sided 95% lower confidence limit for the true proportion of units with residual leukocyte content of less than 5×10^6 per unit is greater than 95%.
- A one-sided 95% lower confidence limit for the true proportion of units with hemolysis at end of storage of less than 1% is greater than 95%.
- Mean 24-hour, post transfusion, *in vivo* red cell recovery at end of storage of at least 75% with standard deviation of at most 9%, and the lower limit of a one-sided 95% confidence interval for the population proportion of successes is 70% or greater.

i) Filtration Recovery Results

Filtration recovery was evaluated for each whole blood processing group filtered with the SOLX® System or the control device. The filtration recovery endpoint, for purposes of this clinical study, was defined as RBC Mass Recovery

Table 5-15 RBC Mass Recovery Results (%)

	Group 1 Test	Group 2 Test	Group 2 Control	---(b)(4)----
Mean	94	94	93	(b)(4)94
SD	2	1	1	(b)(4)
Min	89	91	91	(b)(4)2
Max	99	97	96	(b)(4)
n	60	60	60	(b)(4)
# Units >85% / Total Units	60/60*	60/60	60/60	(b)(4)

*Two (2) Group 1 Test units had inadvertent missed samples at the post-filtration whole blood time point.

* For these two units RBC Mass Recovery was calculated from the additive RBC prepared from the WB unit

Each Test Group processed with the SOLX® System met endpoint criteria for RBC Mass Recovery. The Control Group also met the criteria. The results support that a one-sided 95% lower confidence limit for the true proportion of units with a filtration recovery of red blood cell mass of at least 85% was greater than 95% for each SOLX® System Test Group. The primary study endpoint for RBC Mass Recovery was met.

ii) Processed RBC Leukoreduction Filtration Results

	Group 1 Test	Group 2 Test	Group 2 Control	---(b)(4)-- -
TotalUnits	60	60	60	(b)(4)
Number of Units < 5x10⁶ rWBC in the Total Unites	60/60	60/60	59/60	(b)(4)

The results support that a one-sided 95% lower confidence limit for the true proportion of units with residual leukocyte content of less than 5 x10⁶ per unit was greater than 95% for each SOLX® RBC processing group. The primary study endpoint for leukoreduction was met for each SOLX® group.

The Group 2 Control demonstrated one unit out of 60 that did not meet the criteria for residual WBC per unit and therefore did not meet the 95/95 acceptance criteria.

iii) Hemolysis at End of Storage Results

Table 5-23 Hemolysis (%) on Day 42 of Storage

	SOLX®RBC Group 1 Test	SOLX®RBC Group 2 Test	Group 2 AS-1 RBC Control	(b)(4)
Mean	0.31	0.28	0.40	(b)(4)
SD	0.14	0.08	0.28	(b)(4)
Min	0.09	0.15	0.04	(b)(4)
Max	0.72	0.56	0.98	(b)(4)
n	60	60	60	b(4)
# Units <1.0% / Total Units	60/60	60/60	60/60	(b)(4)

The results support that a one-sided 95% lower confidence limit for the true proportion of units with hemolysis at end of storage of less than 1% is greater than 95% for each SOLX® RBC processing group. The primary study endpoint for hemolysis was met for each SOLX® processing group.

iv) In Vivo 24 Hour Red Cell Recovery Results

There were two *in vivo* data analysis groups in this study, one composed of Group 1 and Group 2 combined *in vivo* results -----(b)(4)-----.

Table 5-26 In vivo 24-Hour Recovery for SOLX®RBCs on Day 42

Day 42		® SOLX RBC Group 1 + 2		--(b)(4)--	
Parameter	Criteria	Single Label n=27	Double Label n=26	(b)(4)	(b)(4)
Mean Recovery (%)	≥ 75%	88.1	86.5	(b)(4)	(b)(4)
SD (%)	≤ 9%	5.8	6.5	(b)(4)	(b)(4)
% LCL for Population Proportion of Successes (# Pass/Total)	≥ 70%	89.5 (27/27)	83.0 (25/26)	(b)(4)	(b)(4)
Study Outcome		Pass	Pass	(b)(4)	(b)(4)

Each SOLX® RBC analysis group (Groups 1+2 ---(b)(4)----) met study acceptance criteria for 24-hour in vivo red cell recovery when assessed for mean recovery, standard deviation and 95% lower confidence limit for the population proportion of successes.

v) In Vivo Red Cell Survival Results

Survival studies were conducted with SOLX® RBC and were not performed with the concurrent control group. There are no recognized criteria for survival of stored red blood cells; therefore the RBC survival studies conducted for this NDA were performed for reference purposes.

Table 5-27 In vivo RBC Survival Studies for SOLX®RBC Stored for 42 Days

Day of Reinfusion	Parameter Mean ± SD	® SOLXRBC Group n=14	® SOLX RBC Group n=13	-(b)(4)-
Day 42	Linear RBC Survival T50(Days)	32 ± 9	35 ± 12	(b)(4)
	Linear RBC Survival Lifespan (Days)	70 ± 20	80 ± 27	(b)(4)

SOLX® RBC demonstrated similar survival parameters for each analysis group. There were no statistically significant differences when comparing SOLX® RBC Groups for survival.

Statistical Review

Based on the reported results, the clinical study showed that the primary endpoints of RBC mass recovery, leukorecution efficiency, hemolysis at end of storage, and 24-hour radiolabeled recovery were met the objective performance criteria for all SOLX®RBCprocessing groups.

In addition to the assessment of primary endpoints of the clinical study, this statistical reviewer conducted the comparative analysis that the sponsor did not perform to investigate the effect of temperature and time of storage on labile coagulation factors.

The review committee of this submission suggested analyzing the results of Factors V, VIII, XI, and Protein S for groups with different process on freezing rate and temperatures:

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(2) Test FFP was the plasma unit derived from Hemerus collection system that was held at room temperature for up to 8 hours post collection before freezing (Group 2);

(3) Control FFP was derived from FDA approved (Hemerus) collection system (Group 2).

Due to the fact that the clinical study of this submission was not designed as paired-sample study, two-sample t-test was performed to compare the coagulation factors between ----- (b)(4) ----- (c) Test FFP and Control FFP.

The results of Coagulation inhibitors (Protein S) and Coagulation factors of Factor V (FV), Factor VIII (FVIII) and Factor XI (FXI) for the comparisons are shown in Table 1 below. The table indicates that the Protein S level and Factor VIII ----- (b)(4) ----- are significantly less than those of Control FFP and Test FFP. Especially, the results of Factor VIII in Table 1 showed highly significant difference as compared to Test FFP. The descriptive statistics of these Coagulation factors are presented in Table 2.

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Table 1. The mean difference of the Hemerus Coagulation Factors: Test - Control (95%CI)
Coagulation Factors for the Test FFP, Test ----- (b)(4) -----, and Control FFP

	Protein S	FV	FVIII	FXI
----- (b)(4) ----- ----- -----	----- (b)(4) ----- ----- (b)(4) -----	(b)(4) -- (b)(4) ----	----- (b)(4) ----- ----- (b)(4) ----- -	(b)(4) --- (b)(4) -----
----- (b)(4) ----- ----- ----- (b)(4) -----	----- (b)(4) ----- ----- (b)(4) -----	(b)(4) -- (b)(4) ----	----- (b)(4) ----- ----- (b)(4) ----- -	(b)(4) --- (b)(4) -----
Test FFP vs. Control FFP	-0.067 (-6.16 , 6.02)	-3.58 (-9.58 , 2.42)	4.62 (-8.5 , 17.73)	0. (-8.16 , 8.36)
Control FFP (n=60): FFP derived from FDA approved collection system.				
Test FFP (n=60): FFP derived from Hemerus collection system.				
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* Statistical significance using 2-sided t-test for the mean difference of two independent				

