



FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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Through: Jaro Vostal, M.D., Ph.D., Chief of LCH
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NDA: BN 110059

Subject: Hemerus Leukosep[®] HWB-600-XL Leukocyte Reduction Filtration
System for Whole Blood with CPD Anticoagulant & SOLX[®] Additive

Sponsor: Hemerus Medical, LLC

REVIEW SUMMARY

The SOLX[®] System is a complete whole blood collection system containing CPD anticoagulant and the proprietary SOLX[®] red blood cell additive solution. The SOLX[®] System is designed with an integrated donor needle, blood diversion bag with integrated blood sampling port, whole blood collection bag, leukoreduction filter, red blood cell storage bag and additive solution bags.

The Army, Hoxworth Blood Center and the University of Maryland have patented the --(b)(4)- formulation and concept. Hemerus has exclusively licensed --(b)(4)-- and received an Army Technology Transfer Initiative (TTI) award to complete the steps necessary to obtain FDA approval. The commercial prototype of --(b)(4)- is called SOLX[®] and is the basis for this NDA submission.

The LEUKOSEP[®] HWB-600-XL Leukocyte Reduction Filtration System with CPD Anticoagulant and SOLX[®] Additive (also called SOLX[®] System) was evaluated for in vitro and vivo performance. In vitro feasibility testing was performed initially followed by in vivo testing conducted under IND 14199.

A tabular listing of clinical studies performed with the SOLX[®] System is presented in Table 5-1. All studies, feasibility and pivotal, were conducted using an identical drug formulation. A prototype leukoreduction filter was used during feasibility studies PC387970 and PC396220. Minor design modifications were made to the leukocyte filter prior to testing in pivotal clinical study PC387580.

Figure 3 – LEUKOSEP® System Diagram

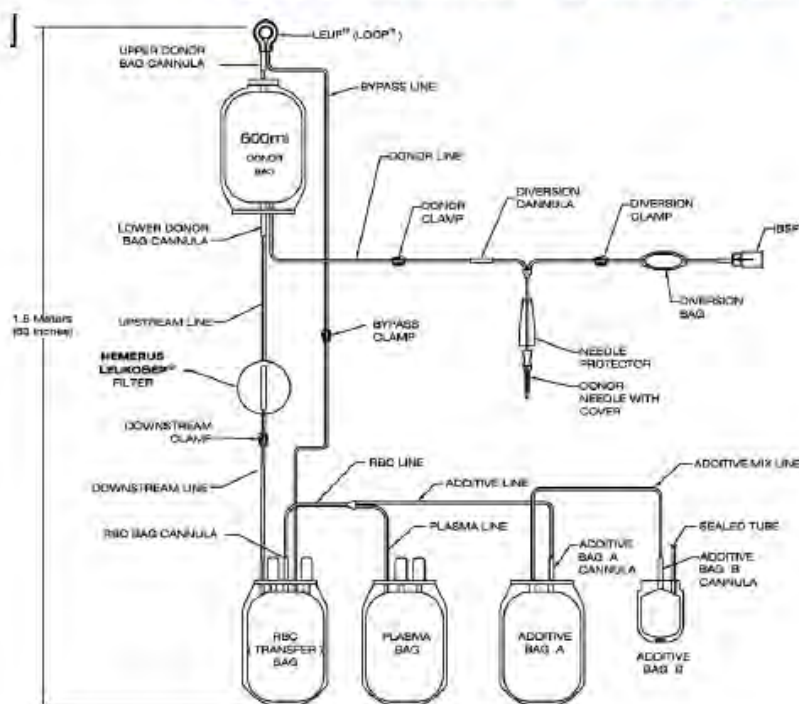


Table 5-1 Listing of Clinical Studies for SOLX® System

Study ID (Year Initiated)	Study Name	Purpose	Number of Subjects	Outcome
PC387970 (2007)	<i>In vitro</i> Feasibility Study of Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive	Feasibility study to test storage of SOLX® RBCs at 6 and (b)(4) weeks of storage as compared to control RBCs stored for 6 weeks.	55 Total 36 Test 19 Control	SOLX® RBCs demonstrated acceptable RBC parameters in support of additional studies.
PC396220 (2008)	<i>In vitro</i> Feasibility Study of Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive	Feasibility study to test storage of SOLX® RBCs at 6 and (b)(4) weeks of storage as compared to control RBCs stored for 6 weeks. Summary of results reported in IND 14199 Section 9.0 Pages 37-42.	24 Total 18 Test 6 Control	SOLX® RBCs demonstrated acceptable RBC parameters in support of pivotal study.
PC387580 (2010)	<i>In vitro</i> and <i>in vivo</i> Evaluation of Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive	Pivotal clinical study to test storage of SOLX® RBCs at 6 and (b)(4) weeks of storage as compared to control RBCs stored for 6 weeks. Plasma studied for up to one year of frozen storage.	240 Total (Subjects Completing All Study Requirements) 180 Test 60 Control	Results of 6 week RBC studies and plasma characterization and stability are the subject of this NDA submission.

Purpose of Study: The pivotal clinical study (PC387580), conducted under IND 14199, evaluated the performance of the LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive also named “SOLX® System”. Three processing groups were studied under different filtration and processing times including RBC and plasma -----(b)(4)-----
----- . The purpose of the study was to support a New Drug Application and subsequent FDA approval for marketing the SOLX® System in the United States.

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”. The protocol was approved by all applicable IRBs, principal investigators and the sponsor, Hemerus Medical, LLC.

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. Objective performance criteria for 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.

Whole Blood Collection

Test and control whole blood units were collected from volunteer subjects meeting all donation and study criteria. Test units were drawn into the investigational product, the Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive. Control units were drawn into a CPD/AS-1 whole blood collection set with integral --(b)(4)-- whole blood leukoreduction filter -----(b)(4)----- . The following Tables show summary of the study results.

Table 5-12 Whole Blood Collection Summary – Subjects Completing Study

	Group 1 Test	Group 2 Test	Group 2 Control	(b)(4)
Unit Volume (mL)				
Mean	572.4	574.0	570.4	
SD	13.3	7.0	12.0	
Min	514.9	559.4	502.0	
Max	601.3	589.4	590.4	
n	60	60	60	
Collection Time (min:sec)				
Mean	07:48	08:11	08:36	
SD	02:26	02:10	02:23	
Min	04:00	04:00	05:00	
Max	15:00	15:25	15:00	
n	60	60	60	
Blood Type (# units)				
O+	27	24	19	
O-	2	3	3	
A+	19	21	25	
A-	3	3	3	
B+	7	6	7	
B-	2	2	1	
AB+	0	1	2	
AB-	0	0	0	

Table 5-22 Processed RBC Leukoreduction Filtration Results

Group	Pre-filtration Mean WBC Content ± SD (cells/unit)	Post-filtration, Post- Processing Mean WBC Content ± SD (cells/unit)	Post- Filtration, Post- Processing Minimum WBC Content	Post- Filtration, Post- Processing Maximum WBC Content	Mean Log ₁₀ WBC Reduction	Number of Units Meeting <5 x 10 ⁶ rWBC/ Total Units
Group 1 SOLX [®] RBC (n=60)	2.9 x 10 ⁹ ± 8.7 x 10 ⁸	1.7 x 10 ⁵ ± 3.5 x 10 ⁵	1.5 x 10 ⁴	2.4 x 10 ⁶	4.6 ± 0.5	60/60
Group 2 SOLX [®] RBC (n=60)	2.8 x 10 ⁹ ± 8.6 x 10 ⁸	1.9 x 10 ⁵ ± 2.5 x 10 ⁵	1.5 x 10 ⁴	1.4 x 10 ⁶	4.4 ± 0.5	60/60
(b)(4)						
Group 2 Control (n=60)	2.8 x 10 ⁹ ± 1.8 x 10 ⁹	4.2 x 10 ⁵ ± 2.5 x 10 ⁶	1.4 x 10 ⁴	2.0 x 10 ⁷	4.6 ± 0.5	59/60

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Table 5-21 RBC Processing Summary

	Group 1 SOLX [®]	Group 2 SOLX [®]	Group 2 AS-1	(b)(4)
RBC Unit Volumes				
Mean (mL)	310.9	311.4	307.7	
SD	18.5	16.9	17.3	
Min	261.0	283.3	277.5	
Max	351.6	359.5	348.0	
n	60	60	60	
Time Placed at 1-6°C Post-Collection				
Mean (hr:min:sec)	02:05:30	07:13:35	07:06:46	
SD	00:56:42	00:22:22	00:17:46	
Min	01:15:45	05:20:00	06:23:22	
Max	05:35:00	08:24:00	08:14:00	
n	59*	60	60	

* One missed measurement.

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	
SD	0.14	0.08	0.28	
Min	0.09	0.15	0.04	
Max	0.72	0.56	0.98	
n	60	60	60	
# Units <1.0% / Total Units	60/60	60/60	60/60	

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	
Mean Recovery (%)	≥ 75%	88.1	86.5	
SD (%)	≤ 9%	5.8	6.5	
% LCL for Population Proportion of Successes (# Pass/Total)	≥ 70%	89.5 (27/27)	83.0 (25/26)	
Study Outcome		Pass	Pass	

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

Day of Reinfusion	Parameter Mean \pm SD	SOLX [®] RBC Group 1 n=14	SOLX [®] RBC Group 2 n=13
Day 42	Linear RBC Survival T ₅₀ (Days)	32 \pm 9	35 \pm 12
	Linear RBC Survival Lifespan (Days)	70 \pm 20	80 \pm 27

Clinical Study Conclusions from the sponsor

All primary study endpoints were met for SOLX® RBC prepared with the SOLX® System and evaluated up to Day 42 of storage at 1-6° C. All SOLX® RBC processing groups met study endpoints including SOLX® RBC processed at ambient temperature and refrigerated within 8 hours -----(b)(4)-----

The following study acceptance criteria were met for each SOLX® RBC processing group:

- 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%.
- 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 was 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% was greater than 95%.
- Mean 24-hour, post transfusion, in vivo red cell recovery at end of storage was at least 75% with standard deviation of at most 9%, and the lower limit of a onesided 95% confidence interval for the population proportion of successes was 70% or greater.

Fresh frozen plasma (FFP) prepared with the SOLX® System and placed at -18° C or below within 8 hours of collection demonstrated comparable levels of plasma proteins (within 20%) as compared to control FFP including: coagulation factors (V, VII, VIII, IX, X, XI and XII), fibrinogen, IgG, Protein C, Protein S, von Willebrand Factor (vWF/Rco) and ADAMTS 13. -----

-(b)(4).

The results of the clinical study support safety and efficacy of the LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System with CPD Anticoagulant and SOLX® Additive when used according to its proposed indications for use:

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- 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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Review Comments and Letter Ready Comments:

1. The sponsor indicated that the study met the acceptance criteria for leukocyte reduction with 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 was greater than 95%. However, FDA identified a leukocyte reduction failure for unit DG3T10 which showed the residual leukocyte of 6.22×10^6 (please see you data.xlsx, under G3 Calc, Postfiltration, line 49 and 50). Please clarify the reason why you do not consider this unit as a failure.
2. Please note the results presented in your “Table 5-22 Processed RBC Leukoreduction Filtration Results” are misleading. Your LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System with CPD Anticoagulant and SOLX® Additive is a Whole Blood leukocyte reduction filtration system. The residual leukocytes present in the “Postfiltration” product should be used for evaluation of the filter performance. Please recalculate the results listed under Table 5-22.
3. Please clarify how did you get the following numbers highlighted in yellow:

[(b)(4)]

[(b)(4)]

4. FDA conducted an analysis of the data you provided for plasma. -----
----- (b)(4) -----
----- . Please note that there is no difference between the Test-
FFP compare to the Control-FFP (Table 1 and Table 2). -----

----- (b)(4) -----

Factor	Test-FFP vs. Control	----- (b)(4) ----- -----	----- (b)(4) ----- -----
FV	-3.58 (-9.58, 2.42)	----- (b)(4) -----	----- (b)(4) -----
FVIII	4.62 (-8.5, 17.73)	----- (b)(4) -----	----- (b)(4) -----
FXI	0.1 (-8.16, 8.36)	----- (b)(4) -----	----- (b)(4) -----
Protein S	-0.07 (-6.16, 6.02)	----- (b)(4) -----	----- (b)(4) -----
Significant result: * two-sided p-value <0.05.			

[(b)(4)]

- a. Retrospective analysis and case reports in the literature suggested an association between the low Protein S activity levels in solvent/detergent-treated plasma (SDP) and venous thromboembolism when SDP was given for thrombocytopenic purpura (TTP) or transfused massively during liver transplantation surgery. This prompted the withdrawal of this product (SDP) from transplantation practice and reinstitution of FFP in the treatment of coagulation factor deficiencies in patients with end-stage liver disease requiring transplantation.
- b. In 2001, the Centers for Disease Control and Prevention (CDC) reported an association between receipt of SDP and death from pulmonary embolism (PE) in liver transplant (LT) patients at Hospital A. The report indicated that intra-operative thromboembolic complications, especially PE, were very rare events prior to the usage of SDP. Hospital A is a non-profit, 1,100-bed hospital, which includes a Liver Disease and Transplantation Center (LT). In 1999, 42 LT were performed at this center; since 1990, 522 LT have been performed. In 1999, the 1-year survival rate in LT recipients was 89.9%. From April 1, 1999, use of SDP in LT patients was begun at Hospital A. From April 2 to December 15, 1999, 6 of 31 (20%) patients undergoing LT procedures at Hospital A developed PE; all 6 died in the operating room (OR). In the previous year, 4 of 37 (11%) patients undergoing LT had died; 3 out of 4 (75%) patients died in the OR. None of the 4 patients had thromboembolic complications, including PE. Because of the association between the adverse events and SDP use, Hospital A personnel reported them to FDA and stopped using SDP on December 15, 1999. FDA conducted an on-site investigation and notified the other U.S. LT centers of the adverse events. In multivariate analysis, the strongest independent predictors of PE incidence were: (1) the quantity of SD Plasma received, and (2) a pre-operative hypercoagulable state. The number of predisposing risk factors for thrombosis remained in the model, although borderline significant ($p = 0.05$). A number of publications reported that SDP has decreased activity levels for Protein S, Protein C, Von Willebrand factor, antiplasmin, and Antitrypsin. According to these reports,

the decrease in coagulation factor activity may have caused thrombosis, and SDP should not be considered as being equivalent to FFP¹.

- c. Buchta et. al. (Vox Sang 2004, 87:182) studied the stability of coagulation factors in thawed, solvent/detergent-treated plasma during storage at 4°C for 6 days and found that the activities of all coagulation factors and inhibitors were at least 0.5 U/mL during storage except for Protein S. Protein S levels decreased from 0.41 U/mL (Day 0) to 0.18 U/mL (Day 6). During storage, the mean levels of Protein S activity decreased to 43% of the baseline values.
- d. Flamholz et. al. (J Clinical Apheresis 2000, 15:169) reported a study of three patients with thrombotic thrombocytopenic purpura exchanged with solvent detergent-treated plasma. The authors indicated “the S/DP plasma has reduced Protein S activity (approximately 0.5 units/mL) as compared with FFP. When used as replacement fluid for repetitive therapeutic plasma exchange, e.g., in patients with TTP, S/DP could lead to lowered Protein S levels and, possibly, risk of hypercoagulable complications.” They concluded, “Our observations suggest that use of S/DP alone or in 50% combination with CSP as replacement fluid in PEX for TTP may lead to difficulty in maintaining safe Protein S levels. Determination of risk of resulting clinically significant thrombotic events requires further study.”
- e. Magner et. al. (J. Cardiothoracic and Vascular Anesthesia, 2007, Vol. 21, No. 3) reported fatal fibrinolysis during orthotopic liver transplantation in patients receiving solvent/detergent-treated plasma (Octaplas).
- f. Hellstern (Hellstern P., Curr. Opin. Hematol. 2004) indicated in his paper that when plasma was stored at room temperature for 15 hours after donation and then frozen, the Protein S activities decreased significantly compared to the plasma frozen 4 hours after collection (Please see Table 1 below). He stated, “On the basis of the results summarized in Table 1, PS activity levels below 60 U/100 mL were found in 21 of 60 RP units frozen 15 hours after collection, but only in 2 of 60 AP units and in none of 100 RP units frozen within 4 hours after donation ($P < 0.0001$, chi-squared test). This may explain why markedly lower PS activity potencies were recently found in Octaplas distributed in Ireland and produced from US RP frozen 15 hours after donation, compared with Octaplas placed on the German market.” -----
----- (b)(4) -----

----- Please note that Runkel et al. (Transfusion March 2005) also presented a similar outcome for plasma held at room temperature for 15 hours (Please see Table 3 below).

Table 1 is quoted from Hellstern P., Curr. Opin. Hematol. 2004

Table 1. Levels of clotting factors, inhibitors, and citrate in blood group A plasma units frozen within 4 h (recovered plasma, RP 4 h) and 15 h (recovered plasma, RP 15 h) after blood collection, respectively, and in blood group A apheresis plasma units frozen within 4 h after collection (AP)

Measure	RP 4 h (n = 100)	RP 15 h (n = 60)	AP (n = 60)	Reference range (n = 100)
FV, U/100 mL	78 (38–166)	72 (18–113)	107 ^a (63–159)	54–145
FVIII, U/100 mL	87 ^d (32–247)	70 (28–148)	93 ^b (52–160)	52–140
FIX, U/100 mL	96 (43–156)	89 (39–152)	121 ^a (69–170)	45–148
FXI, U/100 mL	90 ^e (43–151)	80 (26–154)	111 ^a (66–168)	61–122
Protein S, U/100 mL	87 ^f (51–145)	67 (28–122)	80 ^e (51–106)	56–168
Plasmin inhibitor, U/100 mL	107 (80–215)	102 (87–114)	114 ^c (93–155)	72–132
Citrate, mM	21.8 (19.3–23.3)	20.8 (15.8–23.7)	13.1 ^a (11.9–15)	

Data are expressed as mean value (minimum–maximum).

^a*P* < 0.0001 vs RP 4 h and RP 15 h.^b*P* < 0.001 vs RP 4 h and RP 15 h.^c*P* < 0.0001 vs RP 15 h.^d*P* < 0.001 vs RP 15 h.^e*P* < 0.01 vs RP 15 h.^f*P* < 0.0001 vs RP 15 h.

Table 3 is quoted from Runkel et al., Transfusion. March 2005

RUNKEL ET AL.

TABLE 3. Clotting factors and inhibitors, markers of activated hemostasis and proteolysis, plasma proteins, and citrate concentration in the final plasma bags*						
Measurements	Group 1: AP (n = 60)	Group 2: RP, 3 hr (n = 100)	Group 3: RP, 15 hr (n = 100)	Percentage difference (p value)		
				1 vs. 2	1 vs. 3	2 vs. 3
Clotting factors and inhibitors						
FV (U/dL)	107 (82-137)	74 (53-113)	73 (53-95)	36.4 (<0.0001)	37.7 (<0.0001)	1.3 (NS)
FVIII:C (U/dL)	100 (66-165)	84.5 (50-133)	66 (42-97)	16.8 (0.0002)	40.9 (<0.0001)	12.2 (0.0001)
FVIII:AM (U/dL)	105 (71-150)	87 (53-119)	63 (38-108)	18.7 (0.0001)	50 (<0.0001)	32.2 (<0.0001)
F IX (U/dL)	120 (97-147)	96 (67-121)	87 (62-117)	22.2 (<0.0001)	31.8 (<0.0001)	9.8 (NS)
FXI (U/dL)	107 (82-139)	87 (62-124)	78 (60-100)	20.6 (<0.0001)	31.3 (<0.0001)	10.9 (0.0062)
Fibrinogen (g/L)	2.4 (2-3.1)	2.2 (1.6-3.1)	2.3 (1.6-3.2)	8.6 (NS)	4.2 (NS)	4.4 (NS)
Protein C (U/dL)	94 (72-122)	90 (74-114)	85 (67-101)	4.3 (NS)	10 (0.0035)	6.8 (NS)
PS (U/dL)	87 (63-117)	80 (62-100)	67 (44-93)	8.3 (NS)	25.9 (<0.0001)	17.6 (<0.0001)

5. These plasma products will be transfused to the patients as individual units so it would be important to ensure that individual units contains sufficient amount of coagulation factors and proteins to meet patient needs and to not introduce additional risk. Adequate anticoagulant activity is important, especially in light of the report that TTP patients undergoing plasma exchange with S/D plasma may be more likely to experience deep vein thrombosis as a consequence of low Protein S activity. -----(b)(4)-----.
6. FDA has sought opinions/analyses from cleared, external FDA scientific consultants in developing the content of this letter. -----(b)(4)-----.