



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

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**MEMORANDUM**

NIH Building 29  
Room 330  
Phone: (301) 827-2008  
FAX: (301) 402-2780

**INTERNAL MEMORANDUM**

DATE: March 30, 2012

FROM: Xuan Chi, M.D., Ph.D.  
Lead reviewer  
Laboratory of Cellular Hematology  
DH/OBRR/CBER/FDA  
(301)-827-2008

THROUGH: Jaroslav Vostal, M.D., Ph.D.  
Chief, Laboratory of Cellular Hematology  
Division of Hematology/OBRR/CBER/FDA  
(301)-827-9655

To: Sonday Kelly, M.S.  
Regulatory Project Manager  
CBER/OBRR/DBA  
(301)-827-6122

SUBJECT: NDA BN110059 (The LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive also called "SOLX® System").

**Indications for Use:**

"SOLX® System" is intended for:

- 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

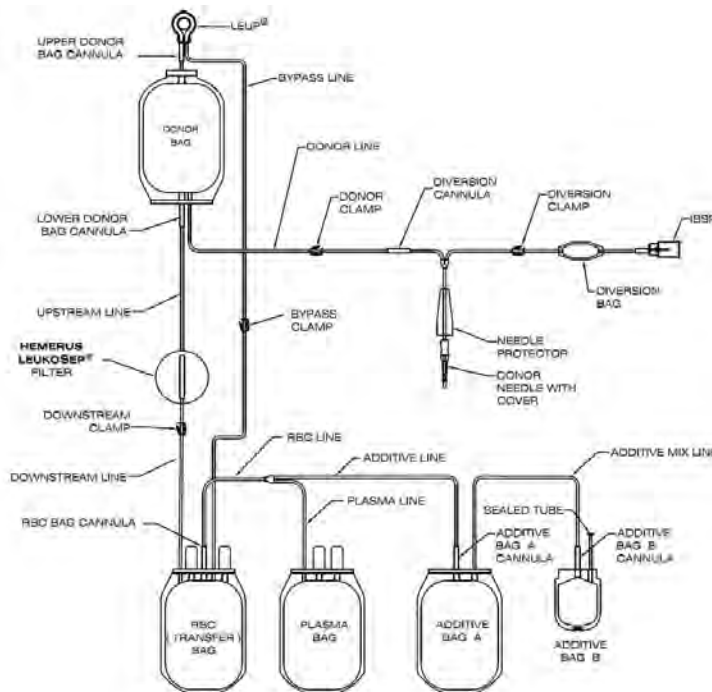
Plasma (FFP), Leukocytes Reduced may be stored at -18° C or below for up to one year after collection.

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(b)(4)

### **Summary:**

HEMERUS Medical, LLC submitted an original NDA for the HEMERUS LEUKOSEP HWB-600-XL Leukocyte Reduction Filtration System for the Whole Blood with CPD anticoagulant and SOLX additive solutions (also called SOLX System). It is designed with an Integrated donor needle, blood diversion bag with integrated blood sampling port, whole blood collection bag, LEUKOSEP® leukoreduction filter, red blood cell storage bag, plasma storage bag and SOLX® additive solution bags. SOLX additive solution is a new red blood cell additive solution.



1. **Clinical studies:** *In vitro* feasibility testing of SOLX system was performed initially (PC387970, PC396220) followed by *in vivo* testing conducted under IND 14199.

1). IND 14199 was conducted at three U.S. investigational sites (Hoxworth Blood Center University of Cincinnati, Dartmouth Hitchcock Medical Center and American Red Cross Mid-Atlantic Research Facility;

2). Three processing groups were studied under different filtration and processing times:

- Group 1 (FFP8hrRT-WB2hr): 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 (FFP8hrRT- WB6hr): 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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3). Results of 6 week RBC studies and plasma characterization and stability are the subject of this NDA submission.

4). Primary endpoints for RBC studies and results

Criteria	Result
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%.	Each Test Group processed with the SOLX System met the endpoint criteria for RBC mass recovery (60/60 successful).
A one-sided 95% lower confidence limit for the true proportion of units with residual leukocyte content of less than $5 \times 10^6$ per unit is greater than 95%.	All SOLX® RBC units from each processing group met study endpoint criteria for RBC, Leukocytes Reduced ( $<5 \times 10^6$ residual WBC/Unit). ----- -----(b)(4)----- -----
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%.	Each Test Group processed with the SOLX® System met the study endpoint criteria for hemolysis. 60/60 (# Units $<1.0\%$ / Total Units) for each testing group.
Mean 24-hour, post transfusion, <i>in vivo</i> 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.	RBCs processed under each study condition and stored in SOLX® additive solution for up to 42 Days met acceptance criteria for <i>in vivo</i> 24-hour red blood cell recovery. The study endpoint for 24-hour <i>in vivo</i> red cell recovery was met for each processing group.

5). Primary endpoints for plasma testings and results

- No primary endpoints for plasma testings were specified.
- Residual WBC content per plasma unit is less than  $5 \times 10^6$ .
- FFP conclusions: Fresh frozen plasma (FFP) prepared with the SOLX® System and placed at  $-18^\circ \text{C}$  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; For data collected to date using  $\pm 20\%$  criteria, SOLX® System FFP demonstrated lower Fibrinopeptide A and TAT Complex at all testing time points and lower C3a and C5a postfiltration as compared to the control FFP.

-(b)(4).

- All 3 month data points were reported, 6 month partial data is completed and 12 month data is on-going.
- 6). BIMO inspection: A BIMO inspection of all 3 clinical sites was requested in November 2011 and the inspection assignment was issued on January 10, 2012 by CBER's Bioresearch Monitoring Branch.
2. **Biocompatibility/toxicology studies** (please see Dr. M. Keith Wyatt's review memo)
3. **Manufacturing sites:**
- LEUKOSEP® HWB-600-XL Leukocyte Reduction Filters for Whole Blood are manufactured at Hemerus facilities in St. Paul, MN.
  - The CPD and SOLX solutions are manufactured and filled into bags at the JMS Singapore facility where the whole blood collection system is also assembled, labeled, sterilized and packaged. CPD anticoagulant and SOLX additive solutions that will be manufactured at JMS Singapore facility will have substantially different manufacturing process (analytical procedures, sterilization) than those products that are listed at the establishment. The JMS Singapore facility is registered with FDA and the Establishment Registration Number is 3002807350. There are 16 products listed under this establishment that include fistula needle, intravascular catheter, administration set and automated blood cell separator. The JMS website lists whole blood collection sets, with and without leukocyte reduction filters as available products in their portfolio. The JMS Singapore facility was inspected by FDA on January 25-28, 2010 and a warning letter was issued on December 15, 2010 for misbranded devices. A request for pre-approval manufacturing site inspection was submitted in November 2011 and a CSO in San Juan District Office, along with a chemist and a biologist are assigned for this inspection. The target completion date is March 26, 2012. This will be the first FDA **drug** inspection of the JMS Singapore site. To date, JMS does not have any drug products on the U.S. market.

**Letter-ready comments**

Please note that the review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission. -----  
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- Please provide 6 month and 12 month plasma testing data when available.
2. Module 2: Please provide a summary of accelerated stability studies for at least 6 months for lot ---(b)(4)----- and lot ----(b)(4)----. Were there any significant changes at any time during the 6 months' testing at the accelerated storage condition? Please also provide a summary of real-time stability data upon completion.
  3. Module 4 (Nonclinical Study Reports):
    - 14-Day Repeat Dose Intravenous Toxicity Study (Module 4, Appendix 4-5): As shown by Table 2, there were 3 blood clotting events in test groups (2 specimens in female test group and 1 specimen in male test group) and 0 clotting event in control specimens. Please explain this result. Both male and female test animals were observed to have significantly lower platelet count ( $p=0.0033$  and  $p=0.0440$  respectively) when compared to controls. The presence of clots within 2 specimens from female mice contributed to the decrease observed in female test group. But in male test group, the specimen with clots was excluded from platelet count. Please explain the decrease in platelet count in male test group.
    - Prothrombin time assay (Module 4, Appendix 4-8): The plasma used for the test article was from multiple donors and the plasma used for the controls was from one of these donors. This is a problematic because donor-to-donor variability will hide potential effects of the tested article on plasma. Both test and control should have been tested using the same lot of plasma/plasmas.
    - The Prothrombin Time Assay study (Module 4, Appendix 4-8) and sister studies Compliment Activation Assay (Module 4, Appendix 4-9) and Unactivated PTT Assay (Module 4, Appendix 4-10) are invalid due to a serious deviation from study protocol (13.0 Protocol deviations). The original study protocol required to bypass the donor bag while introducing the plasma, without mixing plasma with fluids (CPD anticoagulant in donor bag, additive in bag a and b). However, -(b)(4)-- allowed a deviation which resulted in plasma passing through donor bag and came in contact with citrate. This means that citrated plasma was mixed with additional citrate resulting in double amount of citrate in test samples. Since high amounts of citrate are known to change coagulation tests PT and NaPTT, and since citrate dilutes plasma, all three tests are compromised and need to be repeated. In addition,  $n=3$  is not sufficient for coagulation tests.
    - Physicochemical test for plastics-USP (Module 4, Appendix 4-16): DEHP is not dissolved in water. More relevant solvent such as plasma should be used as solvent to extract DEHP.
    - Microscopic Particle Count Test (Module 4, Appendix 4-18): Please specify what guidance was the Evaluation Criteria for the Microscopic Particle Count test based on, or provide justification of the Evaluation Criteria.
    - Transportation Testing Report (Module 4, Appendix 4-25): There were a number of issues identified in this report (Inner box cartons and divider damaged, visual inspection of aluminum foil pack label failed, kinking of collection tubes/connecting tubes, label peel test failed for all 5 groups of blood bags examined). Please provide a summary of corrective actions taken for these issues.