

Summary Basis for Regulatory Action**Date:** April 9, 2013**From:** Xuan Chi, MD/PhD, Chair of the Review Committee**NDA#:** BN110059/0**Applicant Name:** HEMERUS Medical, LLC**Date of Submission:** November 1, 2011**PDUFA Goal Date:** April 28, 2013**Proprietary Name/ Established Name:** SOLX® System / Red Blood Cell Additive Solution 7**Product Name:** The LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive (AS-7) also called “SOLX® System”**Indication:** The LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive (AS-7)* also called “SOLX® System” is intended for the manufacture of:

- CPD/AS-7 Red Blood Cells (RBC), Leukocytes Reduced prepared at ambient temperature and placed at 1 to 6° C within 8 hours of collection. CPD/AS-7 Red Blood Cells, Leukocytes Reduced may be stored at 1 to 6° C for up to 42 days after collection.
- Fresh Frozen Plasma (FFP), Leukocytes Reduced prepared and placed in a freezer at -18° C or colder within 8 hours of collection. Fresh Frozen Plasma (FFP), Leukocytes Reduced may be stored at -18° C or colder for up to one year after collection.

* The SOLX® additive (AS-7) is supplied as two components, 80 mL SOLX® Additive Solution A and 30 mL SOLX® Additive Solution B, combined prior to addition to prepared RBCs.

Recommended Action: Approval**Signatory Authorities Action:****Office Signatory Authority:** Jay S. Epstein, MD, Director, OBRR_____

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Review Discipline	Reviewer Name – Document Date/s
Product Review	Xuan Chi, CBER/OBRR/DH/LCH- Aug 20, 2012 ; Apr 4, 2013 Ping He, CBER/OBRR/DH/LCH - Apr 11, 2012; Apr 2, 2013; Mikhail V. Ovanesov, CBER/OBRR/DH/LH- Aug 23, 2012
Statistical Review	Chinying Wang, CBER/OBE – Jun 6, 2012
CMC Review	Ellen Huang (Sterility/Transportation studies) CBER/OCBQ/DMPQ)- Apr 2, 2013
Pharmacology/ Toxicology Review	M. Keith Wyatt, CBER/OBRR/DH - Mar 20, 2013
Biomonitoring Review	Carla Jordan, CBER/OCBQ - Jun 20, 2012
Establishment Inspection Report	Meloney Jones, CBER/OCBQ/DCM/BDDCB- May 21, 2012
Labeling Review	Lore Fields, CBER/DH/DBA – Mar 29, 2013
Proprietary Name Review	Dana Martin, OCBQ/DCM/APLB – Mar 8, 2013

1. Introduction

This summary basis of regulatory action (SBRA) pertains to a new drug application for a new Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive Solution (AS-7), to be used for the manufacture of CPD/AS-7 Red Blood Cells (RBC), Leukocytes Reduced and Fresh Frozen Plasma (FFP), Leukocytes Reduced.

This document will cover the disciplines of Chemistry Manufacturing and Controls (CMC), Toxicology, Clinical, Statistical and labeling aspects, Establishment inspection, Biomonitoring, and Proprietary name review.

2. Background

HEMERUS Medical, LLC submitted an original NDA for the HEMERUS LEUKOSEP HWB-600-XL Leukocyte Reduction Filtration System for 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, assigned as AS-7 by International Council for Commonality in Blood Banking Automation, Inc. (ICCBBA). Early research and development of a prototype red blood cell (RBC) storage solution called -----(b)(4)----- was conducted by Dr. Tibor Greenwalt (deceased) of the University of Cincinnati and Dr. John Hess of the University of Maryland, formerly of the U.S. Army. The purpose of the research was to develop an improved RBC storage solution that could potentially extend RBC shelf life beyond the current 42 day shelf-life of RBCs with additive solution. The current submission claims a RBC shelf life of 42 days.

The last Red Cell Additive Solution, AS-5, by Terumo BCT, was approved by FDA in 1988.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The Chemistry, manufacturing and control (CMC) section of this application was reviewed by CBER/OBRR/DH/LCH for all CMC sections except sterilization and container closure, and by CBER/OCBQ/DMPQ for the Sterilization and container closure sections.

CMC (except Sterilization and container closure)

- i. The chemical formulation of CPD anticoagulant, SOLX® Additive Solution A and, SOLX® Additive Solution B are described in the table 1:

Table 1 Chemical Formulation of SOLX[®] System Solutions

Solution (Dosage)	Chemical	g/100 ml Solution
Citrate Phosphate Dextrose (CPD) Anticoagulant (70 mL)	-----(b)(4)-----	(b)(4)
	----- (b)(4)-----	(b)(4)
	----- (b)(4)-----	(b)(4)
	----- (b)(4)-----	(b)(4)
SOLX [®] Additive Solution A (80 mL)	---(b)(4)---	(b)(4)
	---(b)(4)---	(b)(4)
	----- (b)(4)-----	(b)(4)
	----- (b)(4)-----	(b)(4)
SOLX [®] Additive Solution B (30 mL)	----- (b)(4)-----	(b)(4)

- ii. The chemical raw materials for CPD anticoagulant, SOLX[®] Additive Solution A and, SOLX[®] Additive Solution B are purchased from suppliers and are all certified as USP compliant chemicals. A Certificate of Conformance is required for each lot of chemical raw materials received. All raw materials are sampled and tested to assure conformance to USP specifications per applicable monograph.
- iii. Hemerus has successfully demonstrated 2-year, real-time stability on three lots of SOLX[®] System product. The stability data support the proposed 24-month expiration date.

Sterilization and container closure integrity and sterility

- i. The primary containers comprising the SOLX[®] System (donor bag, RBC storage bag, plasma storage bag, SOLX[®] Additive A bag, SOLX[®] Additive B bag) are welded PVC bags connected with PVC tubing.
- ii. The SOLX system is terminally sterilized by using a ----(b)(4)----- process at -----(b)(4)-----.
- iii. The NDA submission included the validation of the (b)(4) sterilization process, a re-validation of the (b)(4) sterilization process, the Drug Master File (DMF) on the container and closure for blood bag system, and transportation studies. Container closure and package integrity conforms to FDA Guidance.
- iv. Through an interactive process, the sponsor addressed all issues raised by CBER/OCBQ/DMPQ reviewers satisfactorily.

b) CBER Lot Release

N/A

c) Facilities review/inspection

- i. Hemerus Medical, LLC is the manufacturer of the SOLX® System and sponsor of this NDA submission. The Hemerus facility information is listed below:
Hemerus Medical LLC
5000 Township Parkway
St. Paul, Minnesota 55110
FDA Establishment Registration Number: 3004405714

- ii. JMS Singapore PTE LTD is the contract manufacturer for CPD and SOLX® solutions, finished SOLX® System device assembly, packaging, labeling and sterilization. The JMS Singapore facility information is listed below:
JMS Singapore PTE LTD
440 Ang Mo Kio Industrial Park 1
Singapore, Singapore
FDA Establishment Registration Number: 3002807350

JMS Singapore PTE LTD was inspected by the San Juan District Office beginning on February 24, 2012, and concluding on February 29, 2012. This was the first inspection of the facility as a drug manufacturer. A 13-item 483 related to cGMP deficiencies was issued in areas of product visual inspection procedures and practices, manufacturing operators training, Out of Specifications investigations, environmental monitoring procedures, method validation procedures, supplier certification procedures, microbial bioburden determination procedures and practices, equipment qualification procedures, production procedures review and approval, laboratory equipment qualification and the Corrective and Preventive Action procedures. The firm sent a written response on March 19, 2012, with corrective actions. OCBQ completed review of the Establishment Inspection Report (EIR) and exhibits from the inspection at JMS, as well as the firm's written response and determined that there were no pending issues remaining.

d) Environmental Assessment

All components for AS-7 additive solution are commonly occurring salts that have been used in previously approved Red Cell Additive Solutions. Extensive toxicology studies of the SOLX system were assessed and found acceptable. Based on these data, no adverse impact is expected on animals, plants, humans, other organisms, or ecosystems.

4. Nonclinical Pharmacology/Toxicology

Interactive reviews were conducted on the following Pharmacology/Toxicology studies:

- a) Extensive toxicology studies of the SOLX system were conducted that included the followings:
- *S. Typhimurium* and *E. Coli* Reverse Mutation Assay, Mouse Lymphoma Mutagenesis Assay and Rodent Bone Marrow Micronucleus Assay (ISO 10993-3).
 - Hemolysis Test of Human Blood, Prothrombin Time Assay, Complement Activation Assay, Unactivated Partial Thromboplastin Time Assay, Lee and White Coagulation Test, *In Vitro* Hemocompatibility (ISO 10993-4).
 - Cytotoxicity Test (ISO 10993-5).
 - Kligman Maximization Test and Intracutaneous Injection Test (ISO 10993-10).
 - Systemic Toxicity Test, 14-Day Repeat Dose Intravenous Toxicity Test and Rabbit Pyrogen Test (ISO 10993-11),
- All test results were assessed by the toxicology reviewer and found acceptable.
- b) Studies on the leachables/extractable materials from the container plastics and in-line leukoreduction filter were evaluated and found adequate.
- c) Toxicology studies on ink and labels were assessed and found acceptable.

5. Clinical Pharmacology

N/A, as the final CPD/AS-7 drug dose that is delivered to the patient is not expected to produce a pharmacologic effect.

6. Clinical studies/ Statistical analysis

a) Clinical Program

- i. *In vitro* feasibility testing of SOLX system was performed initially (PC387970, PC396220) followed by *in vivo* testing conducted under IND 14199. A tabular listing of studies performed with the SOLX® System is presented in Table 2.

Table 2

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	<i>In vitro</i> 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.

Study ID (Year Initiated)	Study Name	Purpose	Number of Subjects	Outcome
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	<i>In vitro</i> 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 a 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 mean 24-hour, post transfusion, <i>in vivo</i> red cell recovery at 6 and 8 weeks of storage, <i>In vitro</i> test of SOLX [®] RBCs at 6 and (b)(4) weeks of storage as compared to control RBCs stored for 6 weeks. <i>In vitro</i> test of 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.

ii. Processing groups in clinical studies: Three processing groups were initially 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 SOLX 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. (test units = SOLX solution and filter; control units = -----(b)(4)-----)
- -----

iii. Criteria and results for RBC studies are presented below:

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 5×10^6 per unit is greater than 95%.	<p>All SOLX® RBC units from each processing group met study endpoint criteria for RBC, Leukocytes Reduced ($<5 \times 10^6$ residual WBC/Unit).</p> <p>-----</p> <p>-----</p> <p>----- (b)(4) -----</p> <p>-----</p> <p>-----</p>
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%.	<p>Each Test Group processed with the SOLX® System met the study endpoint criteria for hemolysis.</p> <p>60/60 (# Units $<1.0\%$ /Total Units) for each testing group.</p>
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.

iv. Criteria and results for plasma studies: No primary endpoints for plasma testing were specified. Residual WBC content per plasma unit should be less than 5×10^6 .

FFP conclusions: 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. Reviewers of the plasma studies concluded that the test FFP is comparable to control FFP, and recommended approval.

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

v. **Statistical analysis:**

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 *in vivo* 24-hour radiolabeled recovery were met for all SOLX® RBC processing groups except -----(b)(4)-----
-----.

Due to the fact that the clinical study of this submission was not designed as a paired-sample study, two-sample t-test was performed to compare the coagulation factors between test FFP and control FFP, and showed that test FFP is comparable to control FFP.

vi. **Conclusions for clinical studies:**

Efficacy: Efficacy of SOLX system was demonstrated by successful outcomes in the primary endpoints of post-filtration RBC mass recovery, residual WBC content, hemolysis at the end of storage and 24-hour post transfusion *in vivo* RBC recovery. Comparison of the coagulation factors between test FFP and control FFP showed that factor levels in test FFP were comparable to control FFP.

Safety: The safety profile of the SOLX System for manufacturing of leukoreduced CPD/AS-7 Red Blood Cells and leukoreduced FFP was found to be adequate as judged by toxicology studies and the fact that no serious adverse events (including death) were reported for subjects participated in the clinical studies.

vii. **Biomonitoring**

The clinical studies were 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). The bioresearch monitoring inspections of all three clinical sites did not reveal problems that could impact the data submitted in the application.

b) **Pediatrics**

This application does not trigger PREA (21 U.S.C. 355c) requirements because it does not include new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration.

c) **Other Special Populations**

N/A

d) **Overall Comparability Assessment**

The clinical studies described above revealed that all primary endpoints were met. Extensive toxicology studies of the SOLX system were conducted and results were found to be acceptable. All ingredients of the CPD and AS-7 solutions have been previously approved in other red cell anticoagulant and additive solutions. The final CPD/AS-7 drug dose that is delivered to the patient is not expected to produce a pharmacologic effect. The use of the SOLX® System / AS-7 for the transfusion of leukoreduced CPD/AS-7 Red Blood Cells and leukoreduced FFP poses no additional risks compared to the transfusion of other available leukoreduced Red Blood Cells and FFP. The benefits of leukoreduced CPD/AS-7 Red Blood Cells and leukoreduced FFP prepared with the SOLX® System / AS-7 will be comparable to the benefits of other available Red Blood Cells and FFP.