

Pharmacology Toxicology Review, August 17, 2012 - SOLX® System

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Pharmacology/Toxicology Review

Division of Hematology

Office of Blood Research & Review

TO: The file

CC: Basil Golding, M.D., Director, Division of Hematology, Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER)

FROM: Anne M. Pilaro, Ph.D., Supervisory Toxicologist, Pharmacology and Toxicology Branch, Division of Hematology, OBRR, CBER

NDA #: 110059 and 110059/amendment 14

APPLICANT: Hemerus Medical LLC, St. Paul MN

PRODUCT: HEMERUS LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood, with Citrate-Phosphate-Dextrose (CPD) Anticoagulant and SOLX® Additive

SUBMISSION TYPE: original NDA application, and amendment #14 responding to

FDA information request of June 2, 2012

DATE: August 17, 2012

RECOMMENDATION:

I concur with Dr. Wyatt's conclusions regarding the preclinical findings for the safety of the extractable and leachable components of the SOLX® System, and his current recommendation that this new drug application may not be approved for marketing until additional information is provided to address the risk of thrombocytopenia due to extractable or leachable materials present in the blood components prepared using the SOLX® System. A copy of Dr. Wyatt's review, with supervisory sign-off, has been conveyed to the regulatory project manager for inclusion in the final action package, and has been uploaded into the CBER electronic document room.

SYNOPSIS:

Hemerus has submitted an original NDA application #110059, to support approval of their LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX® Additive, also called the "SOLX® System". The SOLX® System is a complete whole blood collection system containing CPD Anticoagulant and SOLX® Red Blood Cell additive solution, and a filter specifically designed to effectively remove leukocytes, while allowing red blood cells (RBCs) to pass through the media. After filtration, RBCs and plasma are collected into separate, sterile polyvinylchloride (PVC) bags, and 110 ml of the SOLX® additive solution is added to the prepared RBCs as a preservative prior to storage. The proposed indications for the SOLX® System (from the Applicant's draft labeling) are:

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

- 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)-----

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The chemical composition of the CPD and SOLX® Red Blood Cell additive solutions added to the final RBC preparations are provided in Table 1, below (abstracted from Table 2.1, Module 2, Section 2.3.2 of the NDA application). All chemical raw materials used in the manufacture of the CPD and SOLX® Red Blood Cell Additive Solutions meet the specifications for United States Pharmacopeial (USP) grade material (data not shown; Table 3-10, Section 3.2.9.1, Module 3 of the NDA submission). The CPD anticoagulant used in the SOLX® system is formulated to meet the USP requirements (USP Monograph for Citrate Phosphate Dextrose Anticoagulant).

Table 1. Chemical composition of the 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) -----	(b)(4)
SOLX® Additive Solution B (30 mL)	----- (b)(4) -----	(b)(4)

Reviewer Comment: Clinical studies for the SOLX® System were conducted by the Applicant under Investigational New Drug (IND) Application #14199, and the results of these studies were submitted in Module 5 of the NDA. Information regarding the chemistry, manufacturing and process controls involved in the manufacture of the SOLX® System is included in Module 3 of this submission, and the supporting preclinical data are located in Module 4 of the NDA.

Because the SOLX® blood tubing, separation and storage containers, and the leukocyte reduction filter are in contact with the separated RBCs and plasma during the isolation procedure and during storage for up to one year after collection, there was a toxicological concern regarding the potential for chemical leachates or extractable materials into the blood components, and the safety of their subsequent administration to patients receiving RBCs or plasma prepared using the SOLX® System. Therefore, biocompatibility and toxicity testing on the extractable and leachable components of the PVC bags, labels, and inks used on those labels was performed on the various components of the SOLX® System, following the guidelines provided by ISO 10993 – *Biological Evaluation of Medical Devices* and the FDA guidance document *Use of International Standard ISO-10993 Biological Evaluation of Medical Devices Part 1 Evaluation and Testing - May 1, 1995 (G95-1)*. The results of these preclinical tests were included in Module 4 of the original NDA #BN110059 application, and were previously reviewed by Dr. Wyatt in his mid-cycle review, dated April 11, 2012.

The following additional studies, which were submitted by the Applicant on July 26, 2012 as NDA #BN 110059/amendment 14 in response to an Information Request (IR) Letter from CBER dated June 2, 2012 were included in Dr. Wyatt's final review memorandum, and are the subject of this current secondary review:

1. Agar Diffusion Test – Direct Contact with SOLX® Printed Label. (b)(4) Study #12-3101-G1.
2. Resistance of Hemerus Bag Label Prints to Various Liquid Agents. Hemerus Study #PC410930.

The agar diffusion assay evaluated the potential cytotoxicity of the inks used to print the labels for the Hemerus collection and storage bags on cultured mammalian cells, and showed no detrimental effects of direct application of the labels to cultured (b)(4) --(b)(4)---. The second study evaluated the stability of the inks used to print the labels to extraction by either commonly used vehicles in blood transfusion

(normal saline, CPD solution), SOLX® Solution A, -----(b)(4)-----
----- as controls. Dr. Wyatt's review documents that the results of these two assays sufficiently demonstrated that the inks used to print the labeling for the blood bag components of the SOLX® System were stable and non-toxic to mammalian cells, and that this additional information provided by the Applicant was adequate to address the safety issues communicated in the June 2, 2012 IR letter and support approval of the NDA.

However, Dr. Wyatt notes in his current review that a repeat-dose toxicity study testing the safety of the extractable components from the circuits and storage bags that comprise the SOLX® System under its intended conditions of use had identified decreased platelet counts as a remarkable toxicity related to intravenous administration of the extractable/leachate solution. This study ((b)(4) Study #09-5442-G1) was previously reviewed in Dr. Wyatt's mid-cycle review document for NDA #BN110059, dated April 11, 2012, and noted that when compared to the control group, statistically significant, 30% and 50% decreases in mean platelet counts in male and female mice, respectively, occurred after daily, intravenous injections for 14 days of a saline extract of the Hemerus LEUKOSEP® HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood. The Applicant was requested in the June 2, 2012 IR letter to provide an explanation for the decreased platelet counts, and perform histopathology on splenic tissues to rule out any potential immunotoxicity; however, this information was not provided in response to the IR letter. Dr. Wyatt has requested that the Applicant address this deficiency prior to approval of the NDA by providing a risk assessment on potential clinical complications that may be associated with these leachates, specifically regarding the potential to induce thrombocytopenia. This deficiency will be communicated to the applicant in the Complete Review (CR) letter as a requirement to provide a risk assessment, based on data provided in the NDA as well as with data obtained in a supporting, previous study (Study #06-503-N2) of an earlier version of the Applicant's leukocyte reduction system. The Applicant will also be required to identify any significant differences between the earlier leukocyte reduction system used in the prior study and the new SOLX® System, to ensure the relevancy of the results from the previous extraction study #06-503-N2 to the safety of blood components produced with the SOLX® System. Lastly, the Applicant will be advised in the CR letter that an additional preclinical leachable and extractables study and a separate risk assessment for the SOLX® System may be required, if these data cannot sufficiently address the risk.

In summary, Dr. Wyatt has identified an outstanding safety requiring additional preclinical information to be provided by the Applicant, thereby precluding approval. I support Dr. Wyatt's recommendation for a CR letter to be issued, and for the Applicant to provide a risk assessment of the safety of the extractable and/or leachable materials from the circuits and storage bags that comprise the SOLX® System prior to its approval.

Appendix 1. Preclinical studies previously reviewed for this NDA application.

The following preclinical studies were submitted to the original NDA #BN110059, and were the subject of Dr. Wyatt's earlier, mid-cycle review (dated April 11, 2012):

1. ---(b)(4)----- Elution Test. (b)(4) Study #09-3504-G1.
2. Kligman Maximization Test. (b)(4) Study #09-3504-G7.
3. Intracutaneous Injection Test. (b)(4) Study #09-3504-G8.
4. Systemic Injection Test. (b)(4) Study #09-3504-G9.
5. 14-Day Repeat Dose Intravenous Toxicity Study. (b)(4) Study #09-5442-G1.
6. Rabbit Pyrogen Test. (b)(4) Study #09-3504-G10.
7. Hemolysis Human Blood. (b)(4) Study #09-3504-G11.
8. Prothrombin Time Assay. (b)(4) Study #09-3504-G5.
9. Complement Activation Assay. (b)(4) Study #09-3504-G4.
10. Unactivated PTT Assay. (b)(4) Study #09-3504-G6.
11. Lee and White Coagulation Test. (b)(4) Study #09-3504-G3.
12. In vitro Hemocompatibility Assay. (b)(4) Study #09-3504-G2.
13. *S. typhimurium* and *E. coli* Reverse Mutation Assay. (b)(4) Study #09-5442-G2.
14. Mouse Lymphoma Mutagenesis Assay. (b)(4) Study Report #09-5442-G3.
15. Rodent Bone Marrow Micronucleus Assay. (b)(4) Study Report #09-5442-G4.
16. Physicochemical Test for Plastics Report. Study #10-1868-G1.
17. Analysis of Extract for ISO 3826 Test Certificate. Study #06-5803-N2.
18. Microscopic Particle Count Test Report. Study #09-5436-M1.
19. Protocol PC400210. Bench-Top Evaluation of LEUKOSEP® HWB-600-XL Leukocyte Reduction Filter for Whole Blood.
20. Bench-Top Evaluation of LEUKOSEP® HWB-600-XL Leukocyte Reduction Filter for Whole Blood. Report #FR400210.
21. Testing Protocol – Design Verification for SOLX®. TR/105/PED/2007.
22. Testing Report – Design Verification for SOLX®. TR/105/PED/2007.
23. Transportation Simulation Testing. (b)(4) Report #0706135 Rev C.
24. Testing Protocol - Transportation Testing for SOLX®. TP/077/PED/2008.
25. Testing Report - Transportation Testing for SOLX®. TP/077/PED/2008.
26. Testing Protocol – Verification Test on SOLX® Blood Bags with Focus on Blood Bag Labels and Issue on the Sticking of the Interior Walls of the Blood Bag. TP/119/PED/2009.
27. Testing Report – Verification Test on SOLX® Blood Bags with Focus on Blood Bag Labels and Issue on the Sticking of the Interior Walls of the Blood Bag. TP/119/PED/2009.
28. Verification of Foil Pack Integrity of Hemerus LEUKOSEP®/SOLX® System Following Shipment. PC407240.
29. Verification of Foil Pack Integrity of Hemerus LEUKOSEP®/SOLX® System Following Shipment. PC407240.

According to the Applicant and based on the information provided in the study reports cited above and reviewed previously by Dr. Wyatt, all biocompatibility, biochemical, physicochemical and mutagenicity testing met the criteria for acceptance of the safety of the SOLX® system as suitable for its intended use.