



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

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Pharmacology/Toxicology Review  
Division of Hematology  
Office of Blood Research & Review

To: NDA STN #BN110059  
Reviewer: M. Keith Wyatt, PhD, Pharmacologist, CBER\OBRR\DH  
Through: Anne M. Pilaro, PhD, Supervisory Toxicologist, CBER\OBRR\DH  
Sponsor: Hemerus, St. Paul  
  
Product: LEUKOSEP<sup>®</sup> HWB-600-XL Leukocyte reduction filtration system for whole blood with CPD anticoagulant SOLX<sup>®</sup> additive  
Purpose: CRMTS #8746; Type C Meeting request to discuss resubmission, January 17, 2013

Date received: December 13, 2012

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### **Recommendation**

The results from the extractable and leachable studies with the original blood bag containers provide a bridge that is adequate to qualify the safe use of the new SOLX<sup>®</sup> bag, circuits and ports. Because the Applicant has assured that the original leukocyte reduction system and the new SOLX<sup>®</sup> system are comprised of the same materials, from the Pharm/Tox discipline's perspective NDA BN110059 for the SOLX<sup>®</sup> bags and circuits can be approved.

### **Introduction**

Hemerus (the Applicant) submitted an original NDA, STN #BN110059 on October 28, 2011 for the LEUKOSEP<sup>®</sup> HWB-600-XL Leukocyte reduction filtration system for whole blood, with CPD anticoagulant SOLX<sup>®</sup> additive. FDA comments were sent to the Applicant in a CR letter dated August 31, 2012. The Applicant has now requested a Type C meeting (CRMTS #8746) for clarification of FDA toxicology and labeling comments related to BN110059. The Applicant has submitted responses to FDA (Pharm/Tox CR) comments, which have been excerpted and pasted below. FDA follow-up comments appear in **red text**.

**FDA Request (Toxicology – 14 Day Repeat Dose Intravenous Toxicity):**

*Regarding extraction studies on SOLX<sup>®</sup> circuits:*

*The responses you provided in Amendment 14 to BN110059 for FDA questions # 16, 21 b and 24a are not adequate to address the risk associated with the decreased platelet counts observed in mice administered leachate from the circuits and storage bags that comprise the SOLX<sup>®</sup> system. Specifically, your response speculates that the lower platelet count in test animals results from in vitro, spontaneous platelet aggregation. This explanation is not sufficient and this issue remains a safety concern that must be addressed prior to approval.*

Although FDA's question above relates to platelet counts observed in the Repeat Dose Toxicity Study, Questions # 16, 21b and 24a from FDA letter dated June 12, 2012 are presented below for reference purposes.

*16. Regarding additional toxicity test results reported by JMS:*

*The toxicity of PVC manufactured by JMS has not been evaluated by an in vivo implantation assay <USP 88>, or by direct contact and agar diffusion <USP 87> in vitro assays. Please submit results from these.*

*21.b. Regarding extraction procedures used on LeukoSep filters and SOLX circuits: Please justify why an extraction of the LeukoSep filtration unit using an appropriate solvent followed by analysis of the extracts by OC/MS and HPLC/MS was not performed.*

*24.a. Regarding the Repeat-dose toxicity study, 09-5442-G1:*

*Platelet counts in male mice administered SOLX extract following repeat dosing were reduced to  $1075 \pm 147$  KI/-IL compared with  $1374 \pm 45$  K// -IL in saline treated male mice. Platelets were also reduced to  $489 \pm 348$  in female mice administered SOLX extracts compared with  $983 \pm 306$  in female mice administered saline controls. Although sample clotting was observed during this study, please still provide an explanation for decreased platelet counts and perform histopathology on splenic tissues to rule out any potential immunotoxicity.*



(b)(4)



(b)(4)

The ranges of values for each reanalyzed test group are bracketed within the historical ranges for untreated controls. Platelet counts for historical untreated control animals demonstrated relatively high standard deviations and coefficients of variations. This supports the premise that inherent high variability is demonstrated in the testing model for the collection and analysis of platelet counts.

FDA follow-up response, January 7, 2013: Based on the similarity of the historical platelet count data and the recent platelet count data submitted, the Applicant's response is adequate to address the potential safety concerns associated with the platelet aggregation observed during the original repeat-dose toxicity study conducted with the SOLX<sup>®</sup> extract. No additional action by the Applicant is required.

*Spleen Weight Data Analysis*

As part of the 14-Day Repeat Dose Intravenous Toxicity study, spleen weight data for test and control animals were recorded (NDA BN110059 Module 4 Appendix 4-5 (b)(4) Report 09-5442-G1 pages 19 and 20). T-test analysis conducted by Hemerus demonstrated there were no significant differences in spleen weights (total organ weight in grams and relative organ weight in percent) between test and control groups studied. The data are presented in **Tables 4** and **5** below.

(b)(4)

(b)(4)

### Histopathology Analysis

Spleen histopathology was also conducted on test and control animals during the 14-Day Repeat Dose Intravenous Toxicity study (reference NDA BN110059 Module 4 Appendix 4-5 (b)(4) Report 09-5442-G1 pages 24 and 26). There were no noted lesions during histopathology of the spleen for either test or control animals; therefore there were no results for grading of lesions in the histopathology tables found within Report 09-5442-G1. The general histopathology conclusion for organs microscopically examined (adrenal gland, heart, kidney, liver, lung, ovaries, spleen and testis) was stated as, "There were no treatment-related findings in all tissues either in the control or test animals. All findings were incidental spontaneous normal background findings. Based on the macroscopic and microscopic observation, the test article was considered to be non-toxic in this age and strain of mouse after 14 days." ((b)(4) Report 09-5442-G1 page 26).

### Conclusion:

The clarifications and data presented above, including platelet counts, spleen weights and tissue histopathology, support the conclusion of the 14-Day Repeat Dose Toxicity Study stating the test article showed no biologically relevant effects when administered by intravenous injection to mice daily for 14 consecutive days.

FDA follow-up response, January 7, 2013: The Applicant's statistical analysis of spleen weight data and summary of the histopathology results is considered adequate for the purposes of this review, and to ensure patient safety. No additional action by the Applicant is required.



**FDA Request (Toxicology – ISO 3826 Testing):**

*To ensure the safety of the blood components produced using the SOLX<sup>®</sup> system that potentially contain these leachates, provide a risk assessment based on results from the previous extraction study # 06-5803-N2, that was conducted according to procedures described in ISO 3826 on an earlier version of your leukocyte reduction system. Identify any significant differences between the earlier, HRC-600-C Leukocyte Reduction Filtration System for Red Cell (BK070024 8/24/2007) system, and the new SOLX<sup>®</sup> System, to ensure the relevancy of the results from the previous extraction study to the safety of products produced with the SOLX<sup>®</sup> System.*

*Please be aware you may be required to perform an additional leachables and extractables toxicity study and a separate risk assessment for the SOLX<sup>®</sup> System, if any significant differences are identified between the earlier HRC-600-C Leukocyte Reduction Filtration System for Red Cell (BK070024 8/24/2007) system, and we are unable to bridge those data to the new SOLX<sup>®</sup> System.*

**Proposed Hemerus Response:**

The scope of ISO 3826-1:2003 *Plastics collapsible containers for human blood and blood components: Conventional containers* is to specify requirements for plastic collapsible containers for blood and blood components. Although certificate 06-5803-N2 (BN110059 Module 4 Appendix 4-17) lists the test article as “LEUKOSEP<sup>®</sup> Leukocyte Reduction Filtration System for Red Cells” the extraction for chemical analysis was conducted on only the plastic container integral to the system.

The extraction study, summarized with certificate 06-5803-N2, supports SOLX<sup>®</sup> System compliance because the plastic container of the HRC-600-C Leukocyte Reduction Filtration System is comprised of identical materials to the SOLX<sup>®</sup> System containers.

**Table 6** compares the materials comprising the container tested and reported with certificate 06-5803-N2 and the SOLX<sup>®</sup> System containers.

**Table 6 – Certificate 06-5803-N2 Container Material Compared to SOLX<sup>®</sup> System Container**

	Certificate 06-5803-N2 Container Material	SOLX <sup>®</sup> System Container Material
Container (Bag) Material	(b)(4)	(b)(4)
Outlet Port Cover	(b)(4)	(b)(4)
Outlet Port	(b)(4)	(b)(4)
Joint Tube	(b)(4)	(b)(4)

The testing was conducted using guidelines of ISO 3826-*Part 1 Annex A* by (b)(4)

(b)(4)

Additionally, physicochemical testing for the SOLX<sup>®</sup> System was conducted on the dry bag components, tubing and LEUKOSEP<sup>®</sup> HWB-600-XL filter as reported in NDA BN110059 Appendix 4-16 Report 10-1868-G1 *Physicochemical Tests for Plastics*. Nonvolatile residue, residue on ignition, heavy metals and buffering capacity were tested according to USP 32 <661> *Containers, Physicochemical Tests – Plastics*. The SOLX<sup>®</sup> System testing met all criteria contained within the USP guideline.

#### **Conclusion:**

The testing conducted under Certificate 06-5803-N2 and recent testing conducted under Report 10-1868-G1 both support material safety of the SOLX<sup>®</sup> System plastic containers.

#### **10.2.2.1 Questions for FDA – Toxicology**

##### **Question #1 – Toxicology**

The clarifications and data presented above, including platelet counts, spleen weights and tissue histopathology, support the conclusion of the 14-Day Repeat Dose Toxicity Study stating the test article showed no biologically relevant effects when administered by intravenous injection to mice daily for 14 consecutive days.

Based on the foregoing, the clarifications submitted above are intended to adequately address FDA concerns. Does FDA agree with this assessment and resolution?

Based on the similarity of the historical platelet count data and the recent platelet count data submitted, we find your response adequate to address the potential safety concerns associated with the platelet aggregation observed during the original repeat-dose toxicity study conducted with the SOLX<sup>®</sup> bag extract.

The statistical analysis of the absolute and relative spleen weight data and explanation of the histopathology results that you provided are also considered adequate to address our previous safety concerns. No further information is requested at the present time.

**Question #2 – Toxicology**

The container material tested and reported with Certificate 06-5803-N2 is comprised of identical materials to the SOLX<sup>®</sup> System containers. Testing conducted under Certificate

06-5803-N2 and recent testing conducted under Report 10-1868-G1 both support material safety of the SOLX<sup>®</sup> System plastic containers

Based on the foregoing, the clarifications submitted above are intended to adequately address FDA concerns. Does FDA agree with this assessment and resolution?

The nonclinical testing results that qualified the safety of the original leukoreduction blood bag container also provide bridging data that supports the qualification of the SOLX<sup>®</sup> blood bag container, since you have assured FDA that the materials which comprise both the original bag and entire SOLX<sup>®</sup> system, including the circuits, are the same. Therefore, the results generated from the extractables and leachables study conducted with the original blood bag, in addition to the past clinical experience with your original leukoreduction system are adequate to qualify the PVC used in the new circuits, and the filtration unit which constitute the new SOLX<sup>®</sup> system. No additional information is required at this time.