

Summary Basis for Regulatory Action

Date: November 4, 2015

From: Jan Simak, PhD, Chair of the Review Committee

NDA STN Number: BN110059/15

Applicant Name: Haemonetics Manufacturing, Inc.

Date of Submission: February 12, 2015

PDUFA Goal Date: November 15, 2015

Proprietary Name/ Established Name: SOLX[®] System, LEUKOTRAP[®] WB System with CPD Anticoagulant and SOLX[®] Additive Solution

Indication:

Haemonetics' LEUKOTRAP[®] WB System with CPD Anticoagulant and SOLX[®] Additive Solution, also known as the "SOLX[®] System", is indicated for:

- Pre-storage leukocyte reduction of CPD whole blood followed by preparation of AS-7 Red Blood Cells (RBC), Leukocytes Reduced prepared at room temperature and placed at 1 – 6 °C within 24 hours of collection. AS-7 RBC, Leukocytes Reduced, may be stored at 1 – 6 °C for up to 42 days after collection.
- Pre-storage leukocyte reduction of CPD whole blood held at 1 – 6 °C and preparation of AS-7 RBC, Leukocytes Reduced within 72 hours after collection. AS-7 RBC, Leukocytes Reduced, may be stored at 1 – 6 °C for up to 42 days after collection.
- Preparation of Fresh Frozen Plasma (FFP), Leukocytes Reduced prepared from a whole blood collection and frozen at -18 °C or below within 8 hours of collection. FFP, Leukocytes Reduced may be stored at -18 °C or colder for up to one year after collection.
- Preparation of Plasma Frozen Within 24 Hours after Phlebotomy (PF24), Leukocytes Reduced prepared from a whole blood collection. The product can be held at room temperature (RT) up to 8 hours after collection, refrigerated at 1 – 6° C until separated, and placed at -18 °C or below within 24 hours of whole blood collection. PF24, Leukocytes Reduced may be stored at -18 °C or colder for up to one year after collection.
- Preparation of Plasma Frozen Within 24 Hours After Phlebotomy Held at Room Temperature Up to 24 Hours After Phlebotomy (PF24RT24), Leukocytes Reduced prepared from a whole blood collection. The product can be held at room temperature

for up to 24 hours after collection, separated, and placed at -18 °C or colder within 24 hours of collection. PF24RT24, Leukocytes Reduced may be stored at -18 °C or colder for up to one year after collection.

Recommended Action: Approval

Signatory Authorities Action:

Office Signatory Authority: Jay S. Epstein, MD, Director, OBRR

X 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.

Documents for SBRA Development	Reviewer Name – Document(s) Date
Product/CMC Review	Jan Simak, CBER/OBRR/DHRR/LCH 11-04-2015
Clinical Review	Ping He, CBER/OBRR/DHCR - 06-11-2015
Labeling Review	Diane Hall, CBER/OBRR/DBCD/BPB - 10-20-2015
Statistical Review	Zhen Jiang, CBER/OBE - 08-21-2015
Pharmacology/ Toxicology Review	Yolanda Branch, CBER/OBRR/DHCR – 10-20-2105
Sterility/Container Closure Review	Pankaj Amin, CBER/OCBQ/DMPQ – 10-23-2015
Bioresearch Monitoring Review	N/A
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A
Other (list)	

1. Introduction

This summary basis of regulatory action (SBRA) pertains to an efficacy Prior Approval Supplement (PAS) to NDA BN110059, LEUKOTRAP[®] WB System with CPD Anticoagulant and SOLX[®] Additive Solution (the SOLX[®] System) to replace the current leukocyte reduction filter contained within the LeukoSep[®] SOLX[®] System with the Haemonetics whole blood filter (i.e. WBF), and as a result the brand name changed from “LeukoSep” to LEUKOTRAP[®]. The addition of this previously-approved filter allows for an increase in the room temperature whole blood hold time to 24 hours as well as up to a 72-hour cold hold of the whole blood prior to filtration and processing. The subject of NDA BN110059/15, the SOLX[®] System, is a combination product regulated as an NDA.

This document will cover the disciplines of chemistry manufacturing and controls (CMC), clinical, statistical, toxicology, sterility and container closure, and labeling reviews.

2. Background

The SOLX[®] System, approved as NDA 110059 in April 2013, is a complete whole blood collection system containing CPD anticoagulant and SOLX[®] RBC Additive Solution. The product is designed with an integrated donor needle with sharps injury protection features, a blood diversion bag with integrated blood sampling port, a whole blood collection bag, the Haemonetics whole blood filter, a RBC storage bag, a plasma storage bag and SOLX[®] additive solution bags. SOLX[®] additive solution is a RBC additive solution, assigned as AS-7 by the International Council for Commonality in Blood Banking Automation, Inc. (ICCBBA).

The integral WBF is designed to effectively remove leukocytes while allowing RBC to pass through the media. Haemonetics' WBF is presently incorporated into multiple Haemonetics' blood collection systems and was initially approved under NDA BN820915, Supplement 53 and NDA BN800077, Supplement 50 in September 1996.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The Chemistry, manufacturing and control (CMC) section of this application was reviewed by CBER/OBRR/DHRR/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 review)

The SOLX[®] System is a complete whole blood collection system containing CPD anticoagulant and SOLX[®] RBC Additive Solution. The product is designed with an integrated donor needle with sharps injury protection features, a blood diversion bag with integrated blood sampling port, a whole blood collection bag, the Haemonetics WBF, a red blood cell storage bag, a plasma storage bag and SOLX[®] additive solution bags.

The integral Haemonetics WBF is designed to effectively remove leukocytes while allowing RBC to pass through the media. The WBF housing consists of two molded components (body and cap) designed to fit together during assembly. Filter media are sealed within the assembled housing using a process that separates the upstream and downstream filter streams. The filter assembly is attached to inlet and outlet tubes via the inlet and outlet ports of the filter housing.

The Haemonetics WBF is presently incorporated into multiple Haemonetics blood collection systems and was initially approved under NDA BN820915, Supplement 53 and NDA BN800077, Supplement 50 in September 1996. The proposed WBF and the existing filter (Hemerus HWB-600-XL filter) perform in a comparable manner. Table 1 below provides a comparison between former Hemerus HWB-600-XL filter and Haemonetics WBF.

Table 1 Filter Comparison

ELEMENT	FORMER HEMERUS HWB-600-XL FILTER	PROPOSED HAEMONETICS WHOLE BLOOD FILTER (WBF)
Filter Housing (Body and Cap)	(b) (4)	
Media – Upstream Filtration		
Media – Downstream Filtration		

With the exception of the WBF, all components of the proposed SOLX[®] System are identical to the SOLX[®] product approved by FDA under BN110059 in April 2013. Similarly, the packaging of the proposed SOLX[®] System shall remain identical to the SOLX[®] configuration detailed in the original submission of BN110059.

Sterilization and container closure integrity and sterility

With the exception of the filter change, all materials, components and manufacturing processes are the same as currently approved under the SOLX[®] System NDA BN110059 (approval date

April 25, 2013). Further, the proposed, modified, combination product will continue to be assembled, sterilized, packaged, and labeled by the approved manufacturing facility, JMS Singapore. Haemonetics provided adequate justification (report # JST_102997) for considering the current filter in use as the worst case and the replacement filter as not more challenging to the sterilization cycle than the current filter. In addition, the applicant will requalify the sterilization cycle, prior to commercial production runs of the SOLX system with the Haemonetics WBF, p/n 326-92.

The applicant provided the following Post-marketing Commitment:

Haemonetics has been advised that JMS anticipates completion of the sterilization cycle re-qualification activities by December 31, 2015, with availability of their final report by January 30, 2016. Based upon this timeframe, Haemonetics commits to provide the SOLX® sterilization cycle re-qualification report as a Post-marketing Commitment on or before February 19, 2016.

b) CBER Lot Release

N/A

c) Facilities review/inspection

Since this efficacy PAS is for replacement of the leukoreduction filter with the Haemonetics WBF which is currently contained within multiple approved Haemonetics blood collection systems, facility inspections specific to this PAS were not requested.

Haemonetics Corporation is the manufacturer of the SOLX® System and sponsor of this NDA Supplement submission. The Haemonetics facility information is listed below:

Haemonetics Corporation
400 Wood Road
Braintree, MA 02184

FDA Establishment Registration Number: 1219343. FDA performed a facility inspection at the Haemonetics, Braintree, MA location on January 31 – February 7, 2014. The inspection did not result in any Form 483 Inspectional Observation. The Leukocyte Reduction Filter for Whole Blood (i.e. WBF) is manufactured at the Haemonetics facility located in [REDACTED] inspected on [REDACTED]. The inspection did not result in any Form 483 Inspectional Observation.

JMS Singapore PTE LTD is the contract manufacturer for CPD and SOLX[®] solutions, 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. FDA performed a facility inspection of JMS Singapore PTE LTD on February 24 – 29, 2012. The inspection resulted in Thirteen (13) Form 483 Inspectional Observations, related to: 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; equipment qualification procedures; production procedures review and approval; laboratory equipment qualification; corrective and preventive action procedures.

JMS Singapore shall remain the contract manufacturer for the CPD and SOLX[®] solutions, the device assembly, packaging, labeling and sterilization. JMS Singapore continues to maintain a Quality Management System compliant with ISO 13485 and 21 CFR Part 820 FDA Quality System Regulation. A summary of the general processes and facilities participating in the manufacture of the SOLX[®] System is presented in Table 2.

Table 2 Manufacturing processes by facility

Manufacturing Process	Facility Where Process is Performed
Manufacture of Whole Blood Filter	Haemonetics (b) (4)
Manufacture of: - Blood Storage Container - CPD and SOLX [®] Solutions - Assembly, Labeling, Packaging and Sterilization of SOLX [®] System	JMS Singapore PTE LTD Singapore
Verification Inspection and Release of Finished Product	Haemonetics

The SOLX[®] System will be shipped to the Haemonetics [redacted]. The Haemonetics receiving location will verify the SOLX[®] product is received in good condition. Further, Haemonetics will ensure all Certificates of Analyses for the solutions are accompanying the shipment and that they indicate that the results of chemical assays meet acceptance criteria. Upon satisfactory verification, the Haemonetics' [redacted] shall release the product for commercial distribution to end users. Haemonetics Corporation shall maintain oversight of all design and regulatory activities for the SOLX[®] System.

d) Environmental Assessment

All components for AS-7 additive solution are commonly occurring salts that have been used in previously approved RBC Additive Solutions. Extensive toxicology studies of the SOLX system including Haemonetics WBF 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

There were no new nonclinical toxicology studies conducted with the new Haemonetics WBF. The safety of the Haemonetics WBF was qualified based on biocompatibility analysis according to ISO 10093-1:2009 standards. All biocompatibility findings were within acceptable limits, according to ISO-10993-1:2009 standards. These data, together with the longstanding clinical use of the Haemonetics WBF in other, previously FDA-approved Haemonetics blood collection systems, support its safety for use in the Haemonetics LEUKOTRAP[®] SOLX[®] System.

5. Clinical Pharmacology

N/A, as the replacement of the leukoreduction filter is not expected to produce a pharmacologic effect.

6. Clinical/Statistical

a) Clinical Program

***In Vitro* and *In Vivo* Studies of the LEUKOTRAP[®] WB SOLX[®] System**

In vitro and *in vivo* studies of the proposed LEUKOTRAP[®] WB System with CPD Anticoagulant and SOLX[®] Additive Solution were conducted according to Protocol TP-CLN-100331D which was submitted and reviewed by FDA under amendment IND 14199/23 (25) in June 2014. These studies were intended to provide data to support the approval of the Haemonetics LEUKOTRAP[®] Leukocyte Reduction Filtration System for WB with CPD Anticoagulant and SOLX Additive disposable set and to expand the intended labelling to include both a 24-hour room temperature and a 72-hour cold pre-leukoreduction hold.

Study Design and Methods:

The prospective, open label, randomized, controlled, 2-arm, 2-x-2 crossover investigation compared the *in vitro* and *in vivo* performance of the Haemonetics LeukoSep[®] HWB-600-XL

Leukocyte Reduction Filtration System with CPD anticoagulant and SOLX[®] Additive Solution (AS-7) (Investigational Product or IP) to the Haemonetics LEUKOTRAP[®] WB System with CP2D anticoagulant and AS-3 Additive Solution (Control Product or CP). While the IP device provided for this trial was the LeukoSep[®] HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX Additive disposable sets, the objective of the study is to gain approval for the Haemonetics' LEUKOTRAP[®] WB System with CPD Anticoagulant and SOLX[®] Additive Solution, also known as the Haemonetics LEUKOTRAP[®] WBF CPD/AS-7 System, or the SOLX[®] System. Despite the fact that different names are used (LEUKOTRAP[®] and LeukoSep[®]), both IP and CP include the same whole blood leukoreduction filter Haemonetics WBF and differ in anticoagulants and additive solutions only (Table 3).

Table 3 Description of Investigational Product (IP) and Control Product (CP)

	IP	CP
Device	Haemonetics LeukoSep [®] HWB-600-XL Leukocyte Reduction Filtration System	Haemonetics LEUKOTRAP [®] WB System
Whole Blood Filter	Haemonetics WBF	Haemonetics WBF
Anticoagulant	CPD	CP2D
Additive Solution	AS-7 (SOLX [®])	AS-3 (Nutricel [®])
Proposed New Name of the Device	LEUKOTRAP [®] WB System with CPD Anticoagulant and SOLX [®] Additive Solution PN 326-92	N/A

Clinical products used in this investigation consisted of the IP and the CP, both of which are systems designed to collect, leukoreduce, and process 500 mL \pm 10% of whole blood into leukoreduced pRBCs (packed red blood cells) with additive solution and leukoreduced plasma within the closed system.

Arm 1 (n=120; IP=60/ CP=60) entailed holding whole blood units at room temperature after collection for \geq 20 hours and $<$ 24 hours (IP) or \geq 6 hours and $<$ 8 hours (CP) prior to initiating room temperature filtration. Following room temperature centrifugation and subsequent separation of each leukoreduced unit, the pRBC units were placed at 1-6°C and the plasma units were placed at \leq -18°C within 24 hours (IP) or within 8 hours (CP) of collection. RBC storage testing was conducted at 42 day post collection and plasma storage tested conducted after day 30 to represent 1 year frozen storage.

The Arm 1 2-x-2 crossover design included an *in vivo* double-radiolabelled autologous RBC recovery sub-study (n = 24 matched pair IP and CP). An additional evaluation of pre- and post-rejuvenation RBC 2,3-DPG levels was conducted on all Arm 1 IP and CP units. Both the *in vivo* and the rejuvenation studies were conducted only on Arm 1 IP and CP units.

Arm 2 (n= 116; IP=58/ CP=58) entailed holding whole blood units at 1-6°C after collection for ≥ 66 hours and < 72 hours (both IP and CP) prior to initiating cold filtration at 1- 6°C. Following refrigerated centrifugation and subsequent separation of the leukoreduced units, SOLX[®] pRBCs were placed into 1- 6°C storage within 72 hours of collection (both IP and CP). Only pRBC storage testing at 42 days post collection was conducted in this arm.

Acceptance criteria were established for RBC to provide 95% confidence with 95% reliability for:

- WB filtration recovery $\geq 85\%$,
- WB and pRBC rWBC count of $\leq 5 \times 10^6$ / unit,
- Hemolysis at 42 days $\leq 1\%$
- and 95% confidence with 70% reliability for:
 - *In vivo* recovery $\geq 75\%$ with standard deviation $\leq 9\%$.

Results:

WB and pRBC Collection/Processing:

- Filtration recoveries for IP in both Arm 1 and Arm 2 met the acceptance criteria of $\geq 85\%$ for all per protocol and evaluable units when calculated by [redacted] method (Ranges - Arm 1 IP = 87.0 - 94.7% / Arm 2 IP = 91.9 - 94.2%) and the [redacted] method (Ranges: Arm 1 IP = 85.8 - 96.9% / Arm 2 = 87.5 - 106.32%). The primary endpoint to demonstrate 95% confidence in 95% reliability that the IP WB filtration recovery is $\geq 85\%$ was achieved for both Arm 1 and Arm 2. For CP, in both Arm 1 and Arm 2 the WB filtration recovery met the acceptance criteria when calculated by the [redacted] method (Ranges: Arm 1 CP = 90.6% - 93.1% / Arm 2 CP = 90.6 - 94.4%). In two cases (n=2) in Arm 2, the CP did not reach 85% recovery when calculated by the [redacted] method (84.1% and 68.3%). The ranges were Arm 1 CP = 88.4 - 104.0% / Arm 2 CP = 68.3 - 100.7%.
- Post-filtration residual WBC (rWBC) counts for the WB units of the IP in both Arm 1 and Arm 2 achieved the primary endpoint of 95% confidence in 95% reliability $\leq 5 \times 10^6$ / unit in the per protocol and evaluable unit. For the CP, all WB unit rWBC counts were below 5×10^6 / unit in Arm 1 and Arm 2. The primary endpoint to demonstrate 95% confidence in 95% reliability that the IP WB rWBC is $\leq 5 \times 10^6$ / unit was achieved for both Arm 1 and Arm 2.

- Day 42 RBC Hemolysis Primary Endpoint Analysis: The primary endpoint of 95% confidence in 95% reliability for hemolysis $\leq 1\%$ at day 42 after collection was achieved for the IP in all evaluable units. The range for hemolysis at day 42 was Arm 1 IP = 0.11% - 0.87%; Arm 2 IP = 0.09% - 0.87% which is comparable to the literature for 24 hour RT hold. For the CP, all RBC hemolysis data at day 42 were $\leq 1\%$ in Arm 1 and Arm 2. The primary endpoint to demonstrate 95% confidence in 95% reliability that the IP RBC hemolysis at day 42 is $\leq 1\%$ was achieved for both Arm 1 and Arm 2.
- Day 42 RBC *In Vivo* Recovery Primary Endpoint Analysis: The primary endpoint of 95% confidence in 70% reliability for the mean 24-hour post-transfusion *in vivo* RBC recovery $\geq 75\%$ with a standard deviation of $\leq 9\%$ at day 42 was achieved for the IP in the per protocol (n=24) and evaluable units (n=25). The single label () *in vivo* recovery for IP was mean $86.2\% \pm 5.54\%$ and the double label () *in vivo* recovery was mean $86.4\% \pm 6.10\%$, which are comparable to the literature. The single label () *in vivo* recovery for CP was mean $84.4\% \pm 3.70\%$ and the double label () *in vivo* recovery was mean $84.3\% \pm 6.04\%$. The primary endpoint to demonstrate 95% confidence in 70% reliability for the mean 24-hour posttransfusion *in vivo* RBC recovery $\geq 75\%$ with a standard deviation of $\leq 9\%$ at day 42 was achieved for the IP in Arm 1.

Plasma Processing and Storage:

Data from the matched paired population (n = 63) (see Table 4) indicate:

- Extrinsic and intrinsic coagulation pathways PT and aPTT were statistically different between FFP and PF24RT24. The difference in aPTT (intrinsic pathway) may be associated with the reduction in Factor VIII:C in PF24RT24. The difference in PT (extrinsic pathway) may be associated with Factor V trending towards a reduction in PF24RT24. However there are zero occurrences of PT or aPTT being prolonged $> 20\%$ in PF24RT24 compared to FFP so the difference is not likely to be clinically significant.
- Coagulation factors between FFP and PF24RT24 were equivalent except for the expected mean reduction in the labile plasma Factor VIII:C. The labile protein Factor V for PF24RT24 was not significantly reduced compared to FFP but trended towards a reduction.
- Coagulation inhibitors between FFP and PF24RT24 were equivalent except for the expected mean reduction in Protein S which was considered not clinically significant (FFP = 80.4%; PF24RT24 = 74.2%).
- Markers of activation between FFP and PF24RT24 were equivalent.

Table 4. FFP and PF24RT24 Unit Constituents Post Storage

Parameters		Mean (SD)		Median		(Min, Max)		Mean Difference (PF24RT24 - FFP)	
		FFP * (n=63)	PF24RT24 ** (n=63)	FFP (n=63)	PF24RT24 (n=63)	FFP (n=63)	PF24RT24 (n=63)	(95% CI)	P-Value
Intrinsic & Extrinsic Coagulation Pathways	aPTT (secs)	30.25 (2.257)	30.89 (2.237)	30	31	(26.00, 36.00)	(27.00, 36.00)	0.63 (0.21, 1.06)	0.0040
	PT (secs)	11.79 (0.821)	12.05 (0.901)	11.9	12	(9.90, 13.50)	(10.30, 14.00)	0.26 (0.11, 0.41)	0.0011
Coagulation Factors	Factor V (%)	85.14 (16.54)	81.87 (17.18)	82	79	(53.00, 129.0)	(55.00, 132.0)	-3.27 (-6.63, 0.09)	0.0561
	Factor VIII:C (%)	81.00 (22.44)	68.60 (19.71)	78	67	(46.00, 148.0)	(34.00, 118.0)	-12.40 (-16.50, -8.30)	<.0001
	Factor XI (%)	97.02 (11.93)	97.68 (14.04)	98	97	(63.00, 122.0)	(62.00, 137.0)	0.67 (-1.51, 2.84)	0.5420
	vWF/Rco Activity (%)	110.4 (46.88)	103.9 (46.21)	96	89	(45.00, 295.0)	(48.00, 270.0)	-6.48 (-15.24, 2.28)	0.1445
Coagulation Inhibitors	Protein S Activity (%)	80.43 (16.38)	74.24 (15.89)	85	73	(36.00, 112.0)	(39.00, 115.0)	-6.19 (-8.68, -3.70)	<.0001
	Protein C Activity (%)	117.5 (26.22)	118.3 (24.80)	114	113	(72.00, 193.0)	(68.00, 200.0)	0.84 (-4.91, 6.59)	0.7709
	Antithrombin III (mg/dL)	25.63 (2.471)	25.62 (2.406)	26	26	(19.00, 30.00)	(19.00, 32.00)	-0.02 (-0.54, 0.51)	0.9520
Markers of Activation	Factor VIIa (µg/mL)	0.02 (0.023)	0.02 (0.018)	0.013	0.014	(0.01, 0.18)	(0.01, 0.14)	0.00 (-0.00, 0.01)	0.5125
	TAT Complex (µg/L)	4.35 (8.532)	3.05 (2.901)	2.4	2.3	(2.00, 60.00)	(2.00, 18.10)	-1.30 (-3.57, 0.97)	0.2565
	Fibrinogen (mg/dL)	324.2 (58.93)	310.7 (62.80)	319	305	(203.0, 552.0)	(81.00, 427.0)	-13.57 (-30.15, 3.01)	0.1068

* FFP (control group) – manufactured from WB anticoagulated with CP2D and leukoreduced with Haemonetics WBF filter.

** PF24RT24 (investigational group) - manufactured from WB anticoagulated with CPD and leukoreduced with Haemonetics WBF filter.

The occurrences in which PF24RT24 was > FFP by more than 20% and PF24RT24 < FFP by more than 20% provides insight into meaningful differences between PF24RT24 and FFP.

Data from the matched paired population (n = 63) indicate:

- Extrinsic and intrinsic coagulation pathways PT and aPTT showed no occurrences in which PT or aPTT were prolonged in PF24RT24 compared to FFP despite statistical differences in the assay results. These data suggest that there are no clinically meaningful differences between FFP and PF24RT24 for PT or aPTT.
- Coagulation factors between FFP and PF24RT24 were equivalent except for the labile plasma Factor VIII:C and Factor V in PF24RT24 being reduced compared to FFP. The differences observed are considered not to be clinically meaningful. Coagulation inhibitors between FFP and PF24RT24 were equivalent except for the expected reduction in Protein S, which is not clinically meaningful.
- Markers of activation between FFP and PF24RT24 were equivalent except for activated Factor VIIa in which there were more occurrences of PF24RT24 > FFP. However the difference in the assay results was not statistically significant (see Table 4) and probably not clinically meaningful.

Statistical analysis:

Through an interactive process, the sponsor provided satisfactory clarification for all issues raised by the OBE reviewer regarding statistical analysis of the results.

Results for all tested parameters met the acceptance criteria.

Conclusion for clinical studies:

The study results on both Haemonetics LeukoSep[®] HWB-600-XL Leukocyte Reduction Filtration System with CPD anticoagulant and SOLX[®] Additive Solution (AS-7) (IP) and the Haemonetics LEUKOTRAP[®] WB System with CP2D anticoagulant and AS-3 Additive Solution (CP) have met the predetermined acceptance criteria for post filtration RBC recovery, residual WBCs, day 42 hemolysis and *in vivo* radiolabeling studies. Clinical data demonstrate the efficacy of CPD/AS-7 Red Blood Cells and FFP. The product labeling includes a table of FFP and PF24RT24 Unit Constituents Post Storage (Table 4) showing the expected reduction in the labile plasma Factor VIII:C, Factor V, and Protein S in PF24RT24 compared to FFP.

Biomonitoring:

The clinical studies were conducted at two U.S. investigational sites (American Red Cross Midatlantic Blood Services, Norfolk, VA and Hoxworth Blood Center, Cincinnati, OH).

The bioresearch monitoring inspections were not performed for this efficacy PAS studies.

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

This efficacy PAS is for replacement of the leukoreduction filter in the SOLX[®] System with Haemonetics' WBF which is presently contained in multiple approved Haemonetics' blood collection systems. The addition of this filter allows for an increase the room temperature whole blood hold time to 24 hours as well as a whole blood cold hold up to a 72-hours prior to filtration and processing. The preclinical data reveal no toxicological or biocompatibility concerns. Clinical data demonstrate the acceptability of CPD/AS-7 Red Blood Cells and FFP prepared with the SOLX[®] System. The product labeling will include a table of FFP and

PF24RT24 Unit Constituents Post Storage (Table 4) showing the expected reduction in the labile plasma Factor VIII:C, Factor V and Protein S in PF24RT24 compared to FFP.

7. Safety

Safety of the Haemonetics WB filter was qualified based on biocompatibility testing. These data, together with the longstanding clinical use of the Haemonetics WB in other, previously FDA-approved Haemonetics blood collection systems, establish its safety for use in the Haemonetics LEUKOTRAP[®] SOLX[®] System.

8. Advisory Committee Meeting

OBRR reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918]: REFERRAL TO ADVISORY COMMITTEE):

- The SOLX[®] System was approved as NDA 110059 and this efficacy PAS is submitted for replacement of the leukoreduction filter with a Haemonetics' WBF, which is presently a component in multiple approved Haemonetics' blood collection systems and was initially approved under NDA BN820915, Supplement 53 and NDA BN800077, Supplement 50 in September 1996.
- The addition of this filter allows for an increase the room temperature whole blood hold time to 24 hours, as well as a whole blood cold hold of up to 72 hours prior to filtration and processing. Design of the clinical studies to evaluate efficacy of RBC and plasma products collected by SOLX[®] System was adequate. The results of the in vitro and in vivo studies indicate that the transfusion of leukoreduced CPD/AS-7 Red Blood Cells and leukoreduced FFP, PF24, and PF24RT24 prepared with the the SOLX[®] System/AS-7 poses no additional risks compared to the transfusion of other available leukoreduced Red Blood Cells and FFP. The expected reduction in the labile plasma Factor VIII:C, Factor V and Protein S was observed in PF24RT24 compared to FFP.
- BPAC discussion of this application was determined to be unlikely to change the outcome of the scientific review of this application.

9. Other Relevant Regulatory Issues

N/A

10. Labeling

Through an interactive process, the sponsor addressed all FDA issues regarding labeling of the package insert and directions for use. The product labeling will include a table of FFP and PF24RT24 Unit Constituents Post Storage (Table 4) showing the expected reduction in the labile plasma Factor VIII:C and Protein S in PF24RT24 compared to FFP.

Since this efficacy PAS is for replacement of the leukoreduction filter with a WBF contained in previously approved Haemonetics blood collection systems, review of the system's proprietary name was not required.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The recommendation is approval of this efficacy PAS.

b) Risk/ Benefit Assessment

This efficacy PAS is for replacement of the leukoreduction filter in the SOLS[®] System with a Haemonetics' WBF which is a component of multiple approved Haemonetics' blood collection systems.

The safety of the Haemonetics WBF was qualified based on biocompatibility analysis according to ISO 10093-1:2009 standards. These data, together with the longstanding clinical use of the WBF in other, previously FDA-approved Haemonetics blood collection systems, establish the WBF's safety for use in the Haemonetics LEUKOTRAP[®] SOLX[®] System. The addition of this filter allows for an increase in the room temperature whole blood hold time to 24 hours as well as a whole blood cold hold up to a 72-hours prior to filtration and processing. The clinical studies described above revealed that all primary endpoints were met. The expected reduction in the labile plasma Factor VIII:C, Factor V, and Protein S was observed in PF24RT24 compared to FFP. The results of the in vitro and in vivo studies indicate that the transfusion of leukoreduced CPD/AS-7 Red Blood Cells and leukoreduced FFP, PF24, and PF24RT24 prepared with the SOLX[®] System /AS-7 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, PF24, and PF24RT24 prepared with the SOLX[®] System/AS-7 will be comparable to the benefits of other available Red Blood Cells and FFP, PF24 and PF24RT24. The product labeling will include a table of FFP and PF24RT24 Unit Constituents Post Storage (Table 3) showing the expected reduction in the labile plasma Factor VIII:C, Factor V, and Protein S in PF24RT24 compared to FFP.

c) Recommendation for Postmarketing Risk Management Activities

Risk Evaluation and Mitigation Strategies (REMS) were not instituted for this efficacy PAS.

d) Recommendation for Postmarketing Activities

The applicant provided the following Post-marketing Commitment:

Haemonetics has been advised that JMS anticipates completion of the sterilization cycle re-qualification activities by December 31, 2015, with availability of their final report by January 30, 2016. Based upon this timeframe, Haemonetics commits to provide the SOLX[®] sterilization cycle re-qualification report as a Post-marketing Commitment on or before February 19, 2016.