DEPARTMENT OF HEALTH AND HUMAN SERVICES

Summary of Basis For Approval

NDA 040083

Products: NDA 040083 - Anticoagulant Citrate Phosphate Dextrose Solution (CPD) with an integral container of Additive Solution (AS-1) and an integral Leukoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood

Drug Category: Anticoagulant

Sponsor: MacoProductions S.A.S.
c/o Hoppe Regulatory Consultants
2335 Massey Lane
Decatur, GA 30033

Date of Application: November 8, 2004

Related Submissions: IND ------

I. INDICATIONS FOR USE:

The "Leucoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood" is intended for the pre-storage leukocyte reduction of whole blood initiated between 4 and 7 hours after collection if whole blood is stored at ambient temperature, or between 4 and 8 hours of storage at 1 to 6^{o}C. The collection set provides for subsequent preparation of AS-1 Red Blood Cells, Leukocytes Reduced (adenine saline added) and Plasma, Leukocytes Reduced in a closed system. The AS-1 Red Blood Cells, Leukocyte Reduced and Plasma, Leukocyte Reduced may then be stored for the maximum allowable dating periods.

II. DOSAGE FORM:

The Leucoflex MTL1-WB product consists of a whole blood collection system with 70 mL of citrate-phosphate-dextrose (CPD), an anticoagulant for the collection of 500 ± 50 mL of whole blood, and 110 mL of adenine-dextrose-mannitol (AS-1), an RBC preservative solution. They are supplied with sterile, non-pyrogenic fluid pathways. The solution filled systems are ------ sterilized, and the single-unit package contained in a transparent overwrap is ----------.

III. MANUFACTURING AND CONTROLS:

A. Manufacturing and Controls

No new drug substances are involved in this NDA.
The formulations for these products are as follows:

CPD Formulation:

Citric acid ----------, USP	3.27 g
Trisodium citrate----------, USP	26.3 g
------sodium phosphate ----------, USP	2.51 g
Glucose----------	25.5 g
----------	qs to 1000 mL

AS-1 Formulation:

Sodium chloride, USP	9.0 g
Adenine ---------, USP	0.270 g
----------	22.0 g
Mannitol, USP	7.5 g
----------	ad. for -----
----------	qs to 1000 mL

The solutions are manufactured and filled into bags at the MacoProductions S.A.S. facility in Tourcoing, France. All lots of the chemical constituents used in CPD or AS-1 solutions are received from qualified suppliers with a Certificate of Analysis, confirming that the materials confirm to the required specifications. In addition to this Certificate of Analysis, MacoProductions S.A.S. performs on each material all of the tests recommended by the ---------- ---------- the ---------- tests are also done to confirm each of the raw materials used for the CPD anticoagulant solution and the AS-1 additive solution conforms to the relevant monograph. ---------- testing are performed on each lot of incoming raw material. For manufacturing in-process controls, the anticoagulant and additive solutions used in the Leucoflex MTL1-WB leukocyte reduction system are analyzed to ensure the specifications are met.

The raw materials for the container closure system are purchased from ----------. Each of the bags (containers) are made by ------- sheets that are ---------- of material and ---------- known as ----------. There are five types of bags used in the assembly of Leucoflex MTL1-WB leukocyte reduction system:

- ---------- - Bactivam diversion pouch
- ---------- - Collection bag (contains CPD)
- ---------- - Satellite bag (contains AS-1)
- ---------- - Satellite bag (empty at release)
- ---------- - AS-1 RBC bag (empty at release)

B. Stability Studies

Stability data from three production lots of Leucoflex MTL1-WB leukocyte reduction systems containing the drug substances CPD and AS-1 were submitted. The products were studied under normal, accelerated and extreme conditions. The data at this time support a shelf life of 24 months when overwrapped and stored at ----------^{o}C. A use period of ---- days is allowed when overwrap is removed.

C. Methods of Validation

All manufacturing steps, including analytical procedures for drug substances, physical inspections, assurance of sterility, freedom from pyrogens, and holds of the product in quarantine until all requirements for release have been met, are submitted in the NDA file.

D. Labeling

Product labels and Instruction for Use are in compliance with applicable regulations for new drugs.

E. Establishment Inspections

These products are manufactured at MacoProductions S.A.S. facility in Tourcoing, France. The most recent inspection of September 12-21, 2005 found the facility to be in compliance with cGMPs.

F. Environmental Assessment Report

MacoProductions S.A.S. Anticoagulant Citrate Phosphate Dextrose Solution (CPD) with an integral container of Additive Solution (AS-1) and an integral Leukoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood are exempted per under 21 CFR 25.31.

IV. TOXICITY AND PHARMACOLOGY

Leucoflex MTL1-WB leukocyte reduction system consists of primary and secondary bags. CPD is the anticoagulant in the primary bag into which the blood is drawn. The additive solution in a secondary bag is AS-1. The drug substances used in the solutions are well established and approved by the FDA for preservation of whole blood, red blood cells, and plasma components, and demonstrated to be safe and effective by their historic use. Toxicology studies for these drug substances are not necessary.

The collection and storage system is made of a ----------). The product includes an in-line leukocyte reduction filter known as Leucoflex MTL1-WB, storage containers for blood components and tubing, a sample diversion pouch (Bactivam), a vacuum tube

adapter (Vacuvam), and a protective shield for the used needle (Secuvam). The Leucoflex MTL1-WB filter is comprised of a ----------. The following table summarizes the MTL1-WB configuration:

	MTL1-WB
Filtration Configuration	Filtration of Whole Blood
Anticoagulant	CPD
Additive Solution	AS-1
Collection Bag Material	----------
Non-platelet Satellite Bags	AS-1 bag, AS-1 RBC bag, Plasma/FFP bag
Non-platelet Satellite Bag Material	----------
Platelet Bag	No
Platelet Bag Material	NA
Filter	MTL1-WB filter: ---------- ---------- ----------
Tubing	----------
Three-legged Y Connector	No

Biocompatibility Testing of Plastic Materials:

Leucoflex MTL1-WB leukocyte reduction system is an externally communicating device with indirect blood path and contact duration of more than 30 days. The Biocompatibility Testing was performed in accordance with International Standard ISO 10993, Biological Evaluation of Medical Devices, Part I: Evaluation and Testing, and Part 4, "Selection of Tests for Interactions with Blood."

The testing included:

- Cytotoxicity
- Sensitization
- Irritation
- Intracutaneous Test
- Acute and chronic toxicity
- Genotoxicity
- Pyrogen test and
- Hemocompatibility testing
  - Direct Contact Prothrombin Time Test (PT,)
  - Direct Contact Partial Thromboplastin Time test (PTT)
  - Rabbit Blood Hemolysis Test,
  - Direct Contact Human Serum Complement Activation Test.

Testing was performed per the firm's submission to FDA in IND --------- for the MTL1-WB leukocyte reduction systems using product with the designation MTL1-WB---------- as it provided the most rigorous challenge to the biocompatibility program. Testing was conducted by either direct contact of the test article or by a complete interior, fluid path extraction with ------- or ---------- that was subsequently used as the test materials.

All test materials were acceptable. Following tables summarize the results of the non-clinical laboratory testing of the MTL1-WB leukocyte reduction system:

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V. CLINICAL STUDIES

A. Summary of Studies Conducted Using Anticoagulant CPD With an Integral Container of AS-1 and an Integral Leucoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood

A clinical study was conducted on the MacoProductions S.A.S. Leucoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood. The investigation assessed the performance of the MTL1-WB system for leukocyte reduction of whole blood in

order to document that this product meets regulatory guidance with respect to whole blood collection systems with an in-line leukocyte reduction filter.

The in vitro portion of the study was done to evaluate the MTL1-WB system performance in accordance with FDA's guidelines and/or recommendations for blood components. It also compared the performance of the MTL1-WB system to an FDA approved product, CPD/AS-1 collection set with in-line leukocyte reduction filter. Four study sites and two different filtration conditions (filtration on Day 0 at 20 to 24^{o}C with about 5.1 hours of holding time, and filtration on Day 0 at 1 to 6^{o}C with about 5.1 hours of holding time) were implicated. A total of 129 units (91 MTL1-WB, 38 control) were processed for the study. The performance of the Leukoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood was evaluated by measuring the residual WBC per unit after leukocyte reduction filtration, post filtration in vitro RBC recovery of whole blood, and the percent hemolysis immediately post-filtration and pre and post storage of leukocyte reduced RBCs. Biochemical indicators of red cell quality, such as ATP, potassium, sodium, and glucose, were also assessed immediately post-filtration, after preparation of RBCs in AS-1 and at Day 42 following collections.

The in vivo portion of the study was performed at two investigational sites. There were 20 subjects enrolled to assess the 24-hour post-transfusion autologous red blood cell recovery/survival studies of AS-1 Red Blood Cells, which have been collected, leukoreduced and stored for 42 days using MacoProductions S.A.S.'s MTL1-WB system.

The study also includes an objective directed at quality of plasma prepared from the filtered CPD Whole Blood and preserved at minus 25^{o}C or colder for -------- months.

In summary, all study objectives were met, demonstrating successful performance of the Leukoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood, as summarized in Table 1. Additionally, MTL1-WB system produced a red cell units which was similar to that filtered with the FDA approved control system. Thus, it is concluded that the Leukoflex MTL1-WB Leukocyte Reduction System is satisfactory for 21 days storage of CPD leukocyte reduced Whole Blood, and for 42 days storage of leukocyte reduced AS-1 Red Blood Cells following 5.1 (4.1-6.7) hours ambient temperature holding period or following 5.1 (4.6-6.1) hours refrigerated storage prior to filtration. The data generated in the clinical study are presented in the NDA submission, which support a claim that the MTL1-WB system is safe and effective when processed according to product's Instructions for Use.

Table 1: Summery of observed study results:

	Filtration Temperature	
	20 to 24^{o}C	**1 to 6^{o}C**

Holding Time (hours):	5.1 (4.1-6.7)	5.1 (4.6-6.1)
Residual WBC:	n=61	n=30
($x10^6$/unit)	0.417 ± 0.533	0.197 ± 0.131
Observed success rate (%)	61/61 (100%)	30/30 (100%)
RBC post filtration Recovery:	n=61	n=30
Percent	91.1 ± 3.0	89.9 ± 1.9
Observed success rate (%)	59/61 (96.7%)	30/30 (100%)
Hemolysis at 42 days storage:	n=61	n=30
Units with hemolysis <1%	60/61	29/30
Observed success rate (%)	(98.4%)	(96.7%)
RBC in vivo survival/recovery 24 hours post-infusion following 42 days storage:	n=20	NA
Percent	80.2	
SD	4.7	
95% Lower confidence limit	78.4	

B. 24-hour Post-Transfusion In Vivo Recovery/Survival Study of MTL1-WB leukocyte reduction system as used for the Preparation of Whole Blood and Subsequent Preparation of Stored AS-1 Autologous Red Blood Cells

Blood from a total of 20 subjects was used to evaluate 24-hours post transfusion Red Blood Cell Recovery/Survival at two investigational sites. Whole blood was filtered on Day 0, 20 to 24°C, after standing for at least 4 hours at ambient temperature. The filtration was carried out between 4 and 7 hours after collection. AS-1 RBCs and Plasma were prepared after filtration via hard spin at 1 to 6°C. Autologous re-infusion of AS-1 RBCs radiolabeled with both ^{51}Cr and ^{99}Te isotopes performed for units stored for 42 days in the investigational MTL1-WB bags. Red cell recovery/survival tests were performed on samples collected from the donors up to 24 hours after autologous transfusion. The percent of red cell recovery/survival values ranged from 66.0 to 87.0% with a mean of 80.2% and standard deviation of 4.7%, which is above the FDA recommended threshold of ≥ 75% and ≤ 9%, respectively. The lower limit of a one-sided 95% confidence interval for the population proportion of successes is 78.4%, which is above the FDA recommended threshold of 70%. The data gathered in the in vivo studies have shown the performance of the MTL1-WB system to be in accordance with FDA's recommendations regarding the RBC recovery/survival. It is concluded that the in vivo 24-hour post transfusion red cell recovery/survival study for the MTL1-WB system meets FDA's recommendations.

C. In Vitro Studies of the MTL1-WB system as Used for the Collection of Whole Blood and Subsequent Preparation of AS-1 Red Blood Cells and Plasma

a. Leukocyte Reduction

A summary of the results of the performance testing of the MTL1-WB system is shown in Table 1. This summary combines the leukocyte reduction results for units in both the in vitro and in vivo studies. The raw data for each study site were provided in the NDA file as well. In each individual unit the residual leukocyte count was below 5×10^6. The results met the FDA's recommendation that a one-sided 95% lower confidence limit for the true proportion of units with residual leukocytes less than 5×10^6 is greater than 95%.

b. Post Filtration in Vitro Red Cell Recovery

Table 1 summarizes the results of in vitro post filtration RBC recovery results. Individual RBC in vitro recovery values ranged from 78.4% to 96.4%. There were two MTL1-WB units with an in vitro RBC recovery below 85% that were filtered on Day 0 at 20 to 24^{o}C. A statistical analysis of the data showed that the post filtration in vitro RBC recovery met the objectives.

c. Percent of Hemolysis

Percent of Hemolysis data tested at Day 42 after storage are provided in Table 1. Individual percent of hemolysis values ranged from 0.14% to 1.07% when units were filtered on Day 0 at 20 to 24^{o}C; and 0.08% to 1.08% when filtered on Day 0 at 1 to 6^{o}C. There were two units with a Percent of Hemolysis greater than 1%. Based on all the testing, red cell filtration with the MTL1-WB system does not appear to cause any unusual red cell damage as reflected by hemolysis. Furthermore, the degree of hemolysis was not significantly different when compared with the red cells filtrated with the control system after the same period of storage. The Percent Hemolysis criteria have been achieved.

d. Other Indicators of red Cell Integrity and Function

i. Analytical Assays

Additional in vitro indicators of red cell quality and integrity were measured at several time points during the study. Data on the analytes for all time points from all sites are provided in detail in the NDA file for potassium, sodium, glucose, ATP, bicarbonate, pH, pO_2, and pCO_2. Values for all analytes at all time points are comparable for MTL1-WB units versus control units. MTL1-WB filtered red cells appear to maintain their metabolic integrity. Potassium and sodium at the conclusion of storage are comparable when MTL1-WB and control filtered cells are

compared. Glucose consumption, the reduction in glucose between the day of collection and end of storage, does not appear to be impaired. ATP content is maintained at levels similar to those of controls. In addition, the Day 42 ATP level remains at 76% of pre-storage content.

Likewise, bicarbonate and blood gas values were comparable for MTL1-WB units versus the control units as measured during the storage period. As red blood cells consume glucose during storage, the lactic and pyruvic acids accumulate, as a consequence, the pH of the stored blood cells in both MTL1-WB and control units decreased. Additionally, the bicarbonate levels decreases over storage, while the pO_2 levels increase over time. Lastly, the pCO_2 values decrease at the pre-storage time point, and then rise above pre-filtration levels at day 42 measurement points for both systems.

The data from the analytical testing confirm red cell integrity and function are maintained in units collected, filtered and stored with the MacoProductions S.A.S. Leucoflex MTL1-WB leukocyte reduction system.

ii. RBC Morphology

The morphology of human erythrocytes was determined during storage in MTL1-WB and control blood bags. During storage, red cells typically lose their normal discoid shape and can be categorized in four ways; such as smooth disc, crenated disc, crenated spheroid, and total sphere. The score was defined accordingly on a scale of 1 for a smooth disc, 0.8 for a crenated disc, 0.5 for crenated spheroid, and 0.1 for sphere. One hundred red cells were counted and score was totaled. The initial measurement of the red cell morphology, pre or post filtration was a 97.1 mean for MTL1-WB and a 96.1 mean for the control units. The cells were nearly normal, reflecting some collection-related changes. Measurements at Day 42 showed significant changes. The scores were in the 50 to 70 ranges with a mean score of 60.8 for MTL1-WB and 61.1 for control. There was evidence of agglutination as the cells changed their shape. These findings were consistent with no differences between the control units and the MTL1-WB units. The data support the fact that RBC morphological changes are as expected when MTL1-WB unit is used.

iii. Data to Support that the Diversion Pouch Sample Is Not Diluted

During the clinical study, data from 115 collections were analyzed to verify that specimens collected from the Bactivam diversion pouch could be considered undiluted samples suitable for laboratory analysis. The hemoglobin and hematocrit were directly sampled and measured from 115 Bactivam diversion pouches. Pre-filtration hemoglobin and hematocrit

samples were also taken and measured from the corresponding units. A pre-filtration hemoglobin and hematocrit were calculated for each unit as follows:

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(-------)

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The "true" or undiluted hemoglobin and hematocrit are always higher values than those measured on a diluted sample taken from a unit ontaining a solution of CPD in a ratio of 1 part CPD to approximately 7 parts blood. The hemoglobin and hematocrit values on samples from the diversion pouch (presumably undiluted) were then compared to values (back-calculated) as based the weight of the unit and samples taken from the unit (diluted) that were analyzed for hemoglobin and hematocrit. The data summarized in Table 2 support the premise that the Bactivam diversion pouch can provide an undiluted specimen that can be used in the laboratory for testing. Both the hemoglobin and hematocrit sets of results are comparable, within the analytical variability of the methods.

Table 2: Hemoglobin and Hematocrit from Diversion Pouch and Unit

Unit ID	Percent Hematocrit			Hemoglobin (g/dL)		
	Pouch Measured	Pouch Calculated	Pre-filter* Measured	Pouch Measured	Pouch Calculated	Pre-filter* Measured
Mean	41.2	41.2	36.4	14.2	14.0	12.4
S.D.	4.1	4.2	3.8	1.4	1.4	1.2
%CV	9.9	10.2	10.5	9.7	9.8	10.0
Median	41.0	41.1	36.3	14.1	13.8	12.2
Min	31.1	30.6	27.0	10.1	9.6	8.5
Max	50.7	52.3	46.5	17.3	17.2	15.3
S.E.	0.38	0.39	0.36	0.13	0.1	0.1
95% CI	40.5-42.0	40.4-42.0	35.7-37.1	13.9-14.4	13.8-14.6	12.2-12.6
n	115	115	115	115	115	115

* The Pre-Filter sample is taken from the unit after the whole blood has been diluted with CPD.

This indicates that there is no significant dilution of the blood in the Bactivam diversion pouch from CPD in the line.

iv. Influence of Donor Hematocrit and Volume Collected on Primary Endpoints

The primary purpose in collecting a significant number of units with relatively higher numbers of RBCs was to verify that the filter could perform acceptably under these conditions and without excess hemolysis at 42 days of storage. An index, defined as the hematocrit multiplied by the collection volume, was created to assist in the analysis of the data related to hematocrit and collection volume. In this analysis, the units with an index greater than ---- (high RBC mass) were compared to units of minimal RBC mass, that is, having an index of less than ---- (---% hematocrit x 500 mL). Thus the analytical test results of the units with the higher index can be compared to the results of the units with the lower index. The means and 95% confidence limits of both RBC recovery and leukocyte reduction were calculated for each of these subsets, as well as for all of the units collected. The results are presented do not show significant difference between the higher index group and the lower index group.

The groups are:

- 25 units with product of Wt x Vol ≥ ----- (540 mL x --% Hct, upper 20+% of units collected)
- 28 units with product of Wt x Vol ≤ ----- (500 mL x ---% Hct, lower 20+% of units collected)

The data support the conclusion that within these limits, neither volume of units or hematocrit of donor has a significant effect on filter performance based on findings of no significant difference in critical endpoints of the two groups. However, it does reveal the existence of the significant difference between the two groups that when the index ------, post filtration in vitro RBC recovery is lower by weight only. It should also be noted that when looking at RBC recovery in units with lower collection volumes, the effect of the volume of RBCs retained in the filter as a percentage of the total collection volume does influence the recovery calculation in the expected way. The data indicated that there is no significant difference for units containing higher volume of red blood cells, thus demonstrating the effectiveness of the MTL1-WB filter with high volume/high hematocrit units.

D. Plasma Studies

A clinical study was conducted on the Leucoflex MTL1-WB leukocyte reduction

system for investigation of the performance of plasma prepared from the filtered CPD Whole Blood. The objective is to confirm that the plasma is not significantly altered when using the MacoProductions S.A.S. MTL1-WB system, and that Factor VIII and fibrinogen levels are preserved adequately when stored at minus 25°C or colder.

This clinical study was conducted at four different sites and included a total of 178 units of blood (122 MTL1-WB and 56 controls) collected and analyzed from 178 donors. Each participant meeting the site's donor criteria donated 500 ± 50 mL blood, which was collected in 70 mL of CPD. Investigational and control units were processed according to the protocol and filtered either under ambient (20 to 24°C) or cold (1 to 6°C) conditions. Immediately post-filtration and prior to freezing, the performance of the MTL1-WB system was evaluated by measuring residual WBC per unit, platelet counts, albumin, C3a and C5a in post filtered plasma. For fresh frozen plasma product, units were filtered at 20 to 24°C, separated within 8 hours of collection and stored at minus 25°C or colder. The fibrinogen and Factor VIII studies at 6 and 12 months are conducted on the 20 to 24°C filtration cohort only, which is comprised of 61 MTL1-WB and 28 control samples. Analysis of these data, summarized in Table 3, supports the fact that the plasma components were not significantly altered during the collection and filtration process.

Table 3: Post Filtration Plasma Summary of Results

		Residual WBCs ($x 10^6$)/unit	**Platelets ($x 10^6$)/unit**	**Albumin (mg/mL)**	**C3a (ng/mL)**	**C5a (ng/mL)**
MTL1-WB	**Mean**	0.05	94	33.8	532	3.06
	Median	0.03	0	35	498	2.89
	Min	0.02	0	10	130	0.58
	Max	0.28	2720	53	1788	6.77
	S.E.	0.00	NA	0.56	20	0.14
	95% CI	0.04-0.05	NA	32.7-34.9	493-571	2.78-3.34
	n	122	120	120	122	122
Control	**Mean**	0.06	95	32.9	782	3.01
	Median	0.03	0	34	713	2.79
	Min	0.02	0	10	377	0.42
	Max	0.50	1626	44	2575	6.86
	S.E.	0.01	NA	0.81	51.1	0.21
	95% CI	0.04-0.08	NA	31.3-34.5	680-885	2.60-3.43
	n	56	56	56	56	56

NA = Not applicable to platelet data

The units filtered on Day 0 at 20 to 24°C, with plasma separated within 8 hours of collection, were also analyzed post filtration for factor VIII and fibrinogen. Factor VIII and fibrinogen laboratory results were adjusted to account for dilution

caused by the presence of 70 mL of CPD in the collection bag. Each result provided by the sites (from a diluted plasma sample) was multiplied by ----------. It is worth mentioning that the laboratories performing the testing for fibrinogen have different reference ranges. Table 4 lists summarizing data of the post filtration results for fibrinogen and Factor VIII. The conclusion from the MTL1-WB data is that Factor VIII and fibrinogen are present in sufficient quantity in post filtration plasma samples.

Table 4: Post Filtration Plasma Summary of Fibrinogen and Factor VIII Results

		Fibrinogen (mg/mL) and reference range				**Factor VIII IU/mL**
		Site 1 (------)	**Site 2 (---------)**	**Site 3 (----------)**	**Site 4 (--------)**	
MTL1-WB	**Mean**	3.01	3.23	3.61	3.62	1.51
	Median	3.04	3.13	3.78	3.47	1.47
	Min	1.85	2.13	1.23	2.85	0.49
	Max	4.43	4.76	5.20	5.44	2.64
	S.E.	0.20	0.15	0.36	0.16	0.06
	95% CI	2.55-3.46	2.91-3.53	2.79-4.44	3.28-3.96	1.40-1.62
	n	10	21	10	20	61
Control	**Mean**	4.13	3.05	3.91	3.52	1.76
	Median	4.07	2.86	3.95	3.44	1.50
	Min	3.15	2.18	2.60	2.49	0.88
	Max	5.25	4.51	5.14	4.35	3.27
	S.E.	0.51	0.24	0.52	0.20	0.12
	95% CI	2.53-5.75	2.50-3.59	2.26-5.57	3.07-3.97	1.51-2.00
	n	4	10	4	10	28

Results adjusted for CPD dilution

These same plasma units filtered on Day 0 at 20 to 24^{o}C and separated within 8 hours of collection were then stored at minus 25^{o}C or colder to produce plasma that is defined as fresh frozen plasma (FFP). Samples of the FFP were pulled after six months of storage and tasted for Factor VIII and fibrinogen content. 60/61 samples had a Factor VIII level greater than 0.5 IU/mL. Sixty of 61 MTL1-WB units had fibrinogen level equal to or above the lower limit of the reference interval. The results at six months storage showed the lower limit of the one-sided confidence limit was 95.7% for both fibrinogen and Factor VIII. It is also evident from the data that there were no significant differences between the test and control for both variables. Table 5 summarizes the results, indicating successful performance of the MTL1-WB system on FFP products.

Table 5: Summary of Six Month Stability of Fibrinogen and Factor VIII Results

	Fibrinogen (mg/mL) & reference range	**Factor VIII**

		Site 1 (--------)	Site 2 (---------)	Site 3 (---------)	Site 4 (--------)	IU/mL
MTL1-WB	**Mean**	3.16	3.66	3.76	3.55	1.38
	Median	3.22	3.53	3.93	3.23	1.39
	Min	2.06	2.44	2.48	2.58	0.38
	Max	4.63	5.24	5.12	5.99	2.54
	S.E.	0.20	0.17	0.25	0.20	0.06
	95% CI	2.70-3.63	3.31-4.01	3.19-4.33	3.13-3.96	1.26-1.50
	n	10	21	10	20	61
Control	**Mean**	4.14	3.63	3.99	3.45	1.68
	Median	4.21	3.34	4.06	3.39	1.54
	Min	3.22	2.73	2.86	2.47	0.65
	Max	4.19	5.55	4.96	4.24	3.13
	S.E.	0.42	0.31	0.43	0.19	0.11
	95% CI	2.80-5.47	2.92-4.43	2.61-5.36	3.03-3.88	1.46-1.91
	n	4	10	4	10	28

Results adjusted for CPD dilution

Factor VIII and fibrinogen values were determined on plasma after 12 months of storage (see Table 6) at minus 25^{o}C or colder in units that were separated within 8 hours and qualify as FFP. After 11 to 15 months of storage at minus 25^{o}C or colder, all 61 samples had Factor VIII values greater than 0.5 IU/mL without anticoagulant in MTL1-WB units. For all sites combined, the Factor VIII values ranged from 0.73 to 2.54 IU/mL. At 12-month storage, fibrinogen values equal to or greater than the lower limit of the testing facility reference interval without anticoagulant was 61 of the 61 MTL1-WB units. The lower limit of the one-sided confidence limit was 95.2% for both variables (fibrinogen and Factor VIII), which is greater than the FDA's recommended threshold of 95%. It is also evident that there are no significant differences between the MTL1-WB filter versus control filter with regard for Factor VIII or fibrinogen at 12 months.

Table 6: Summary of 12 Month Factor VIII and fibrinogen Stability Results

	MTL1-WB		Control	
	Factor VIII IU/mL	**Fibrinogen mg/mL**	**Factor VIII IU/mL**	**Fibrinogen mg/mL**
Mean	1.41	3.68	1.70	3.65
Median	1.33	3.64	1.58	3.64
Min	0.73	2.08	1.06	2.58
Max	2.54	5.81	2.61	5.83
S.E.	0.05	0.10	0.10	0.16
	1.33	3.52	1.54	3.38
95% CI	1.32-1.51	3.49-3.87	1.50-1.90	3.2-3.98
n	61	61	27	27

Results adjusted for CPD dilution

Overall, the factor VIII and fibrinogen content appeared to remain stable from the time it was measured immediately post filtration, to the six month and twelve month test points. The Leucoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood produces a plasma product meets recommended threshold for Factor VIII and fibrinogen after twelve months of storage at minus 25^{o}C or colder.

VI. CONCLUSION

The above data support the safety and efficacy of use of Leucoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood for pre-storage leukocyte reduction of whole blood initiated between 4 and 7 hours after collection if whole blood is stored at ambient temperature, or between 4 and 8 hours of storage at 1 to 6^{o}C. The subsequent AS-1 Red Blood Cells, Leukocytes Reduced and Plasma, Leukocytes Reduced have been proven safe and effective for their intended use when stored for the maximum allowable dating periods. RBC in vivo and in vitro values were satisfactory following storage of CPD whole blood and AS-1 Red Blood Cells. Coagulation factors appear stable in plasma stored for up to one year in frozen state at minus 25^{o}C or colder.

These results suggest that Leucoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood for pre-storage leukocyte reduction of whole blood is suitable for use in the collection and storage of rd blood cells and Fresh Frozen Plasma.

Date:

_____

Ping He, M.D.
Medical Officer
Review Committee Chairperson
Division of Hematology
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Date:

_____

Sukza Hwangbo, R.Ph., D.A.B.T.
Device Review Branch,
Division of Blood Applications
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Date:

Jaroslav Vostal, M.D., Ph.D
Chief of Laboratory of Cellular Hematology
Division of Hematology
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Date:

Basil Golding, M.D.
Director
Division of
Office of Blood Research and Review
Center for Biologics Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FINDING OF NO SIGNIFICANT IMPACT
FOR
APPROVAL OF A NEW DRUG APPLICATION
FOR THE MANUFACTURE OF
LEUCOFLEX MTL1-WB LEUKOCYTE REDUCTION FILTER
FOR WHOLE BLOOD FOR PRE-STORAGE LEUKOCYTE REDUCTION
OF WHOLE BLOOD

The review committee has carefully considered the potential environmental impact of this approval and has concluded that the Environmental Assessment for Categorical Exclusion requested by the MacoProduction is acceptable. Under 21 CFR 25.31, Human drugs and biologics, action on NDA can be exempted from environmental assessment if the action does not increase the use of the active moiety or if the action does not significantly alter the environment. The introduction of MacoProductions S.A.S. Leucoflex MTL1-WB Leukocyte Reduction Filter for Whole Blood meets these requirements and exclusion from the preparation of an environmental assessment or an environmental impact statement.

No significant adverse environment effect/risk is expected to result from the production or use of this product. The manufacture and distribution of the product does not generate or emit pollutants or materials considered to be biohazardous. All waste materials are disposed of in accordance with Federal, State and local environmental requirements.

Therefore, the committee finds no significant impact on the environment as a result of this approval.

Date: _____

Ping He, M.D.
Medical Officer
Review Committee Chairperson
Division of Hematology
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Date: _____

Sukza Hwangbo, R.Ph., D.A.B.T.
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Division of Blood Applications
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Center for Biologics Evaluation and Research

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Division of
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