Summary Basis of Approval
OB-NDA 00-0127

Product: Citrate Phosphate Double Dextrose (CP2D) & Additive Solution 3 (AS-3)

Company: Haemonetics Corporation
400 Wood Road
Braintree, MA 02184

Date of Application: January 21, 2000

I. Indication for Use:
The 250 mL CP2D anticoagulant and 250 mL AS-3 nutrient solutions are intended to be used only with automated apheresis devices for collecting human blood and blood components. Anticoagulant is metered by the apheresis machine into the collected whole blood. It is not to be infused directly into the donor. After the anticoagulant is used, the bag in which it was contained is discarded. When collecting plasma in the RBCP protocol, the plasma is collected into an empty plasma collection bag. 100ml of AS-3 is transferred into one RBC collection bag when using the RBCP protocol or 2 separate bags when using the 2RBC protocol. AS-3 solution provides nutrients to keep the red blood cells viable for 42 days when refrigerated.

The 300 mL AS-3 will be used in conjunction with automated red cell washing devices. AS-3 serves as the nutrient solution for storage of the red blood cell product after deglycerolization. The red blood cells are washed using the Model 215 System. AS-3 is used for priming the disposable and for the last wash of the red cells. Then the washed cells are resuspended in 100 mL of the AS-3 before transfer into a product collection/storage bag. AS-3 provides nutrients to keep the washed red blood cells viable for up to 14 days after washing when refrigerated.

Neither the CP2D nor AS-3 containers are used for the storage of blood or blood components.

II. Dosage Form:
The container for all CP2D and AS-3 solutions is a flexible polyvinyl chloride (PVC) bag sized for holding the appropriate amount of solution. The bag has a single port that is used for bag filling. The port is sealed after filling with a male luer assembly (CP2D) or female luer assembly (AS-3). Both the male and female luers are gamma irradiated prior to use. The plastic bag is contained in an overwrap which is added prior to sterilization.

III. Manufacturing and Controls:

A. Manufacturing:

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

CP2D

Each 100 mL contains:

Citric Acid (Monohydrate), USP	0.327 g
Sodium Citrate (Dihydrate), USP	2.630 g
Monobasic Sodium Phosphate (Monohydrate), USP	0.222 g
Dextrose (Anhydrous), USP	4.640 g

AS-3

Each 100 mL contains:

Citric Acid (Monohydrate), USP	0.042 g
Monobasic Sodium Phosphate (Monohydrate), USP	0.276 g
Sodium Chloride, USP	0.410 g
Adenine, USP	0.030 g
Dextrose (Anhydrous), USP	1.000 g
Sodium Citrate (Dihydrate), USP containing 15 mEq of Sodium.	0.588 g

The plastic bags are made by ----------. The solutions are manufactured and filled into bags at the Haemonetics Corporation facility in Union, SC. Testing is performed on the environment, raw materials, in-process and finished products to assure that appropriate requirements and specifications are met.

B. Stability Studies:

Data was submitted on three lots of 250 mL CP2D and 250 and 300 mL AS-3 held at room temperature for 18 months and at 40^{o}C for 6 months. ----------
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C. Methods of Validation:

All critical manufacturing steps, including sterilization and all systems have been successfully validated and are part of the NDA.

D. Labeling:

Draft labeling has been submitted. No trade name is being used. The Directions for Use are contained in the appropriate apheresis machine manual.

E. Establishment Inspection:

The Union, SC facility had a Pre-Approval Inspection for.CP2D and AS-3 December 4 through 7, 2001.

F. Environmental Impact Statement:
CP2D and AS-3 are exempted per under 21 CFR 35.31(a).

IV. Pharmacokinetics and Bioavailability:
CP2D and AS-3 have been approved and manufactured by Medsep Corporation for many years under OB-NDA 82-915. Further, the use of CP2D as a whole blood anticoagulant and of AS-3 as a nutrient solution is well documented in the literature. Since no new drug substances are involved in either CP2D or AS-3, no additional pharmacological or toxicological studies have been conducted in animals or humans for CP2D or AS-3 manufactured by Haemonetics. References regarding CP2D and AS-3 are included Section 14of the NDA.

V. Clinical Data:
Studies of the effectiveness of 250 mL CP2D and 250 mL AS-3 made by Haemonetics Corporation Union, South Carolina facility included *in vivo* survival data in healthy subjects at one test site and *in vitro* characterization of stored red blood cells at three test sites.

Haemonetics Clinical Evaluation #95012, involved autologous *in vivo* recovery and survival studies, and *in vitro* red cell characterization, conducted at a single site. RBC results collected with Haemonetics CP2D/AS-3 were compared to crossover controls of manually collected RBCs from the same donors using CP2D/AS-3 made by Medsep Corporation (crossover manual controls). In addition, results were compared to data from other RBC apheresis donors and using CP2D/AS-3 solutions manufactured by MedSep (unmatched apheresis controls). Test parameters included hematocrit, hemoglobin, RBC and WBC counts, ATP levels, pH, supernatant potassium, free hemoglobin, supernatant glucose levels, and product weight. The RBC quality of test units after 42-day storage was equivalent or slightly superior to those of the control units. RBCs collected by the two different collection protocols (Red Cells with or without Plasma) showed no significant differences in terms of RBC quality and red cells from all groups met FDA and AABB guidelines for 24-hour recovering at 42 days storage.

Study #98001 was performed using 250 mL CP2D and AS-3 to confirm *in vitro* the results of Clinical Evaluation #95012. Three test sites each performed three RBCP and three 2RBC apheresis procedures using the MCS+ LN8150 and associated collection sets. In addition, each site collected six manual whole blood units as concurrent (unmatched) controls using Medsep sets, and prepared RBCs according to standard procedures.

In vitro tests of red cell functional and physical integrity were conducted at Days 0 and 42 of storage. All plasma units from the RBCP and manual procedures were evaluated on Day 0 for *in vitro* product characteristics. Group t-tests (two tailed) were performed to examine any statistically significant differences between the properties of apheresis and manual RBCs. Statistically significant differences ($p<0.05$) were evaluated in terms of clinical significance. Differences in glucose or lactate levels, hematocrit, pH, and supernatant potassium were not considered clinically relevant, because these parameters have not been found to correlate significantly with the *in vivo* 24 hour % recovery.

The results from this study confirmed the observations from Clinical Evaluation #95012. The quality of stored RBC products collected by apheresis is similar to RBC products collected manually. A difference in ATP and hemolysis levels, both after processing and on day 42 of storage, for the apheresis units were not statistically significant when compared to ATP and hemolysis levels from manually collected RBCs and were similar to historical reference values.

300 mL AS-3 was used in conjunction with an automated closed system, the Haemonetics Model 215 (now called the ACP) in Clinical Evaluation #97002. Five test sites were used in this study. 100 samples were tested *in vitro* and 30 *in vivo*. Red blood cells derived from CPDA-1 whole blood units were used. AS-1 red blood cells were used as a control. A total of 140 red blood cell units were glycerolized and deglycerolized. The *in vitro* RBC quality and *in vivo* RBC viability data obtained on these units demonstrate that red cell units glycerolized and deglycerolized using the Model 215 System and resuspended in 300 mL AS-3 solution manufactured by Haemonetics, Union, South Carolina are processed in a closed system and can be stored for 15 days at 4°C.

VI. Safety and Efficacy:

Haemonetics is unaware of adverse reports or recalls of either CP2D or AS-3 solution in plastic bags which would bring the safety of these products into question. These products have been used for whole blood collection in the US since 1982.