SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1.0 GENERAL INFORMATION

1.1 Generic Name: Density Gradient Separation Medium

1.2 Trade Name: DACS^{TM}SC Kit

1.3 Applicant Name and Address

Dendreon Corporation

3005 First Avenue

Seattle, WA 98121

1.4 PMA Number: BP97-0003

1.5 Date of Panel Recommendation: None

1.6 Date of Notice of Approval: 23 July 1999

2.0 INDICATIONS FOR USE

BDS60 is indicated for the processing of autologous mobilized peripheral blood progenitor cells (PBPC) collected by leukapheresis to reduce red blood cells, platelets and granulocytes in the final PBPC product. Autologous PBPC, which have been processed using BDS60, are capable of hematopoietic reconstitution following myeloablative therapy. It is recommended that sufficient leukapheresis product be collected to provide at least 2 x 10^6 CD34+ cells/kg of patient body weight after BDS60 processing.

BDS60 is not indicated for use with other stem cell products, specifically umbilical cord blood and bone marrow (see **CONTRAINDICATIONS**).

3.0 DEVICE DESCRIPTION

DACS^{TM}SC is a kit that contains five separate components for processing of autologous PBPC by buoyant density centrifugation. One kit is sufficient to process a single autologous, mobilized PBPC apheresis collection.

- Buoyant Density Solution 60 (BDS60): 135 ml of a buoyant density solution containing colloidal silica and supplied in a glass bottle.
- DACS Separation Container: A cylindrical device (Diameter 3.8 in., Height 4.75 in., Volume 450mL) with a funnel shaped silicone insert dividing the Container into

upper and lower chambers. The container is designed to hold up to a maximum of $5x10^{10}$ nucleated cells in a 250 mL plasma-poor apheresis product volume. The container is comprised of _____ and a silicone insert.

- Tubing Set A: A 36 inch long tube that has a filtered air-vented spike on one end for insertion into the BDS60 glass storage container and a luer lock on the other end for attachment to the Separation Container. Tubing Set A is comprised of _____ _____ luer lock and spike components.

- Tubing Set B: A 36 inch long tube that has a spike on one end for insertion into the leukapheresis bag and a luer lock on the other end for attachment to the Separation Container. Tubing Set B is comprised of _____ _____ luer lock and spike components.

- Tubing Set C: A 36 inch long tube that has a luer lock on one end for attachment to the Separation Container and a luer lock on the other end for attachment to a bag for cell washing. Tubing Set C is comprised of _____ _____ clamp and luer lock components.

Principles of Operation

- BDS60 solution: The density of BDS60 is such that CD34+ cells accumulate at the buffer-BDS60 interface while the bulk of nucleated cells are located in the pellet after centrifugation at 850 x g for 30 minutes at 20°–25°C.

- DACS Separation Container: The Container has a funnel shaped silicone insert that separates cells at the BDS60-buffer interface from cells in the pellet. The insert traps pelleted cells in the lower chamber of the container thereby allowing harvest of the interface cells by decantation.

- Tubing Set A is designed to transfer BDS60 from its glass storage container to the Separation Container.

- Tubing Set B is designed to transfer cells from a leukapheresis bag to the Separation Container.

- Tubing Set C is designed to transfer cells from the Separation Container to a bag for cell washing after processing with BDS60. Depending upon the specific bag selected by the user, additional adapters may be required for cell transfer with Tubing Set C.

4.0 CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

BDS60 is not indicated for use with stem cell products other than peripheral blood progenitor cells (PBPC). Specifically, BDS60 is not formulated for processing of bone marrow or cord blood products.

BDS60 is not formulated to process previously frozen apheresis products.

Warnings

It is recommended that a sufficient number of cells be harvested during leukapheresis to provide for infusion of at least 2 x10^6 CD34$^+$ cells per kg of patient body weight after processing. Failure to infuse an adequate number of CD34+ cells can result in delayed engraftment of neutrophils and platelets, and potential engraftment failure. On average 20-30% of the CD34+ cells are lost during the separation process (see **9.0 SUMMARY OF CLINICAL STUDIES, Tables 2 & 3**). If at any time the user believes that the CD34+ cells necessary for engraftment are in the non-target fraction in the lower Separation Container (see Attachment 1; **Harvest and Wash the Cells**, page 8), that fraction may be collected using strict aseptic technique according to the procedure on page 8 (see Attachment 1; **Optional Cell Recovery From Lower Separation Container).** *Do not reprocess cells recovered from the lower chamber.*

All components are intended for single use only.

Do not use bottles and containers with a broken seal or with leakage.

Precautions

Maintain aseptic conditions and perform cell processing using sterile technique.

Process cells in a biological safety cabinet/laminar flow hood.

Handle all human specimens as if they are infectious.

Dispose of all specimens and tubes in compliance with current regulations for biohazardous materials.

5.0 ALTERNATIVE PRACTICES AND PROCEDURES

As an alternative to removal of granulocytes, platelets and red blood cells by BDS60 gradient separation, the plasma-poor apheresis product containing PBPC may be directly infused or cryopreserved for subsequent infusion without further separation or removal of unwanted cellular elements.

There is no existing device directly comparable to BDS60. [redacted] the DACS SC system and BDS60 have not been investigated for or shown evidence of the ability to remove tumor cells contaminating an autologous PBPC product.

6.0 MARKETING HISTORY

DACS™SC has not been marketed in the United States or any foreign country.

7.0 ADVERSE EFFECTS

7.1 Adverse Effects of the Device on Health

Contamination of the PBPC preparation with bacteria or fungi during processing

Among PBPC products processed with BDS60 using DACS™SC plasticware, there was no evidence of bacterial (n = 17) or fungal (n = 16) contamination after processing. Twenty-six PBPC products processed with BDS60 using 50 mL conical centrifuge tubes were tested for bacterial contamination. One PBPC product that was negative prior to processing became culture positive (*Staphylococcus aureus)* after BDS60-processing. The subject who received these cells did not develop evidence of sepsis.

Impairment of Engraftment

The time to hematopoietic reconstitution and the risk of delayed engraftment following myeloablative therapy supported by PBPC infusion are related to the number of CD34+ cells infused (see **4.0 WARNINGS)**. In the clinical efficacy study, all subjects were infused with $\geq 2 \times 10^6$ CD34+ cells/kg. One of the 46 subjects who received BDS60-processed PBPC experienced delayed platelet engraftment (defined as failure to achieve a platelet count ≥20,000/µl by day 18 post-PBPC infusion). None of the 46 subjects experienced delayed neutrophil engraftment (defined as failure to achieve an absolute neutrophil count ≥ 500 µL by day 14 post-PBPC infusion (see **9.0 SUMMARY OF CLINICAL STUDIES, Table 1)**.

7.2 Potential Adverse Effects of the Device on Health

Infusional toxicity associated with residual BDS60 in the PBPC product

[redacted] As described in Section 8.2, animal toxicology studies have shown no

toxicity following administration. [redacted] During clinical testing there were no clinically significant adverse events or laboratory abnormalities associated with infusion of PBPC isolated using BDS60.

Device and performance failures

No mechanical or performance failures (as evidenced by failure to partition the cell populations in the Separation Container) have been reported. There is the potential for performance failures, resulting in insufficient recovery of CD34+ cells in the upper chamber. In this event, follow procedures in Attachment 1 under Harvest and Wash the Cells, page 8, to attempt recovery of sufficient numbers of CD34+ cells from the separated PBPC product.

8.0 SUMMARY OF PRECLINICAL STUDIES

8.1 Laboratory Studies

The objectives of the laboratory studies of the DACS™SC were to evaluate the following:

- Effect of undiluted BDS60 on mobilized human peripheral blood mononuclear cells
- Effect of diluted BDS60 on mobilized human peripheral blood mononuclear cells
- *In vitro* toxicity of BDS60 on rabbit and human serum, plasma, and whole blood.

Effect of undiluted BDS60 on mobilized human peripheral blood mononuclear cells

The effect of undiluted BDS60 on hematopoietic progenitor cells from mobilized human peripheral blood mononuclear cells was examined *in vitro* on apheresis samples (n=11) from G-CSF treated cancer patients. This effect was defined by counting the number of total cells, CD34+ cells and colony forming (clonogenic) cells before and after mixing and incubation of the mobilized human peripheral blood sample for 30 minutes. Five different lots of BDS60 were tested. Total cell recovery and viability was determined by counting cells in the presence of Trypan Blue. The recovery and number of cells that expressed CD34 antigen were determined by fluorescence- activated cell staining analysis. The capacity of the hematopoietic progenitor cells contained in the cell preparation to proliferate and form colonies *in vitro* was determined.

No significant loss of total cells, CD34+ cells and colony forming cells (CFU) was detected.

In a separate study (n=2), the effect of BDS60 on cells centrifuged immediately or incubated four hours before centrifugation was evaluated. Mobilized PBPC were layered

on BDS60 and incubated for 0, 2, or 4 hours at room temperature. After incubation, the cells were centrifuged for 30 minutes and recoveries of total cells, CD34+ cells and CFU at the interface were determined. Compared to zero and two hours, the total cell recovery increased after incubation for four hours. Incubation for two or four hours did not significantly increase or decrease the recovery of CD34+ cells or CFUs compared to cells centrifuged immediately (zero hours).

Effect of diluted BDS60 on mobilized human peripheral blood mononuclear cells

In a similar study, the effect of 1:6 diluted BDS60 on mobilized human peripheral blood mononuclear cells was examined *in vitro* on four apheresis samples from G-CSF treated cancer patients. The effect was defined by counting the number of total cells, CD34+ cells, and clonogenic cells before and after mixing and incubation of the mobilized human peripheral blood sample for four hours in 1:6 diluted BDS60.

No significant loss of total cells, cells that express CD34 antigen, or total CFU was observed.

Effect of BDS60 to induce hemolysis in human or rabbit blood

The hemolytic potential of BDS60 in human blood or rabbit whole blood was assessed by incubation of undiluted or 1:10 or 1:100 dilutions of BDS60 (in 0.9% saline) at 37°C for 30 minutes. Spectrophotometric analysis (540 nm) of the amount of hemoglobin in the supernatant revealed that the undiluted test article caused a slight amount of hemolysis of human whole blood, whereas 1:10 and 1:100 dilutions caused no hemolysis. When this analysis was repeated, no hemolysis of human whole blood was observed with undiluted or diluted BDS60.

Undiluted and diluted rabbit whole blood exposed to BDS60 did not hemolyze at any concentration tested.

Effect of BDS60 to induce flocculation in human or rabbit plasma or serum

The compatibility of BDS60 with plasma and serum samples isolated from healthy humans or rabbits was assessed. Equal volumes of plasma, serum or vehicle were mixed with BDS60, followed by a 30-minute incubation at room temperature, with subsequent evaluation for precipitation or coagulation. No precipitation or coagulation was observed upon macroscopic or microscopic examination of plasma or serum in any of the samples, nor were any pellets observed when samples were centrifuged.

8.2 Animal Studies

The objectives of the animals studies described below performed with BDS60 were to evaluate the following:

- 14-Day acute intravenous toxicity of BDS60 in rats

- Antigenicity of BDS60 in guinea pigs by systemic anaphylaxis
- Pyrogenicity of BDS60 in rabbits (USP Rabbit Pyrogen Test)

14-day acute intravenous toxicity of BDS60 in rats

A single intravenous injection of 0.02, 1.0, or 5.0 mL/kg of BDS60 or 5.0 mL of 0.9% saline (control) was administered to rats. Evaluations for 14 days included clinical signs, body weights, and gross observations.

No deaths or abnormal clinical observations, body weight changes, or gross findings were evidenced in any animal at any dose level or lot number of BDS60. The estimated acute intravenous LD_{50} in rats was greater than 5.0 mL/kg.

Antigenicity of BDS60 in guinea pigs by systemic anaphylaxis

Sensitization Phase - Twelve guinea pigs were intraperitoneally injected with 0.25 mL of one of six different lots of BDS60, once weekly for four weeks. Five positive control animals received ovalbumin (OVA) at 200 µg/mL and ten negative control animals were administered 0.9% saline. The first dose for all test article and control groups was mixed with an equal volume of 20% adjuvant, while the last three doses contained undiluted test article or respective control material.

Rechallenge Phase - Two weeks after the last sensitization dose, the positive control animals were challenged with an intravenous administration of 10 mg of OVA. The test-article-sensitized animals were challenged with 0.25 mL of the lot of BDS60 to which they had been sensitized. The negative control groups were also challenged with BDS60.

All five of the animals immunized with OVA died of apparent anaphylactic shock when challenged. None of the animals challenged with BDS60 showed any sign of anaphylaxis.

USP Rabbit Pyrogen Test

Each lot of BDS60 is tested for pyrogens by intravenous injection into rabbits (10 mL/kg) according to the US Pharmacopoeia. Every lot has been non-pyrogenic and there has been no acute toxicity.

Toxicity of DACS™SC components

The potential toxicity of BDS60 and the plasticware devices used in conjunction with BDS60 were assessed in animals in tests that reflected planned use of BDS60 as part of the DACS™SC kit. All parts of the DACS™SC Kit's Separation Container (plasticware and silicone insert) that could potentially come into contact with the patient's blood cells were exposed to BDS60. The BDS60 was then injected intravenously into mice and intracutaneously into rabbits. In both tests, the BDS60 extract was not toxic.

The Separation Container and plastic tubing sets provided in the DACS^{TM}SC kit are prepared with Class VI materials as listed in 3.0 Device Description. Extracts of the plasticware were evaluated for toxicity according to the US Pharmacopoeia. Polyethylene glycol (PEG400) and sesame oil extracts were injected intraperitoneally into mice; saline and ethanol/saline extracts were injected intravenously into mice; and sesame oil, saline and ethanol/saline extracts were injected intracutaneously into rabbits. In each of these tests, the plasticware extracts were non-toxic.

9.0 SUMMARY OF CLINICAL STUDIES

9.1 Primary Efficacy Study

Protocol Title: A Phase I/II Trial to Determine the Safety and Efficacy of the ACT CD34+ Cell Enrichment Kit to Enrich Mobilized Peripheral Blood Progenitor Cells for Reconstitution of Hematopoiesis following Myeloablative Chemotherapy in Breast Cancer Patients

Study design

The safety and device performance of BDS60 for processing mobilized, autologous peripheral blood progenitor cells (PBPC) was evaluated in a single arm, two site (University of Chicago and Weiss Memorial Hospital) clinical trial.

The primary endpoint was to assess the engraftment rate of BDS60-processed PBPC. Secondary endpoints were device performance (the recovery of total nucleated cells [TNC] and CD34+ cells in the BDS60-processed PBPC product), assessment of device and performance failures, assessment of durability of engraftment, and assessment of adverse events associated with infusion of BDS60-processed PBPC. After discussions with FDA, the primary efficacy endpoint was revised at the Agency's request, to assess time to neutrophil and platelet engraftment and to demonstrate lack of clinically significant delays in median times to engraftment as compared to a reference group.

The inclusion criteria were:

- Histologically documented high risk Stage II or IIIa or IIIb adenocarcinoma of the breast or chemotherapy sensitive Stage IV adenocarcinoma of the breast for which high dose chemotherapy and autologous hematopoietic support is indicated.
- Age 18-60 (physiologic)
- Karnofsky Performance Status: >70%
- Life expectancy: >six (6) months
- At least four (4) weeks since major surgery or radiation therapy.
- Required initial laboratory data:

Granulocytes	> 1,500/mm^3
Platelet count	> 100,000/mm^3
Hemoglobin	> 9 g/dl
Creatinine	< 1.8 mg/dl
Bilirubin	≤ 1.5 x upper limits of normal

- Informed Consent
- No previous or concurrent malignancy, except inactive non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer if the patient has been disease-free for ≥ five (5) years.

The exclusion criteria were:

- Pregnant or lactating (at risk female subjects must have a negative serum pregnancy test). All sexually active patients must practice a medically acceptable form of birth control.
- Inadequate venous access for leukopheresis.
- Presence of any acute or chronic medical condition, organ dysfunction or laboratory abnormality that may increase the risks associated with study participation or interfere with the interpretation of study results.
- Treated with another investigational agent within four (4) weeks prior to enrollment.

PBPC were collected by leukapheresis after the patients were mobilized with filgrastim and chemotherapy. One or more leukapheresis products were processed with BDS60 to ensure that each patient received at least 2 x 10^6 CD34+ cells per kilogram. The PBPC products were processed with BDS60 solution used in conjunction with one of two centrifugation plasticware systems. BDS60-processed PBPC were infused intravenously one day after completion of myeloablative chemotherapy.

Post-transplantation, patients were assessed for toxicity due to infusion of BDS60-processed PBPC and for hematopoietic reconstitution (engraftment). The vital signs (temperature, pulse, respiration, blood pressure) of the first twenty patients were monitored hourly for the first four hours after PBPC infusion and then every four hours for the next day. Complete blood counts were monitored daily to determine when the

infused PBPC had reconstituted the bone marrow. Neutrophil engraftment was defined as more than 500 neutrophils/mm^3 ("sustained" ANC >500). Platelet engraftment was defined as the first of three consecutive days with a platelet count of ≥20,000 platelets/mm^3 in the absence of a platelet transfusion in the preceding 24 hours.

Analytic plan:

Descriptive statistics were to be generated for the incidence and severity of infusional toxicity and of late toxicities. Time-to-event analyses were to be performed for neutrophil and platelet engraftment. The proportion of subjects with delayed neutrophil engraftment (ANC >500/mm^3 on or after day 14) or delayed platelet engraftment (platelets >20,000/mm^3 on or after day 18 were also assessed.

In addition, a retrospective analysis was performed, in which the engraftment characteristics of the study subjects were compared to an historical reference group. This reference group consisted of 12 women with breast cancer who had undergone autologous transplantation with unprocessed PBPC at the study sites over a 2-year period immediately preceding the clinical trial. The reference group was selected based on the infused dose of CD34+ positive cells ($\geq 2x10^6$/kg) and the progenitor source (peripheral blood).

Amendments to the study

Three different device configurations were utilized in sequential cohorts of patients during the course of the clinical study: (a) 50ml conical centrifuge tube with a silicone trap insert supplied prefilled with BDS60, (b) the same 50 ml centrifuge tube supplied dry and with BDS60 supplied in a glass bottle, and (c) the DACS Separation Container as described herein.

Study Results

Patient demographics

Fifty-one women were enrolled in the trial. Their mean age was 47 years (range: 30 -64).

Patient Disposition, Dropouts

Leukapheresis products from 47 patients were processed with BDS60; three patients failed to mobilize sufficient CD34+ cells and one patient withdrew before leukapheresis. A total of 59 PBPC leukapheresis products were collected and processed with BDS60. Of these 59 PBPC products, 17 were processed with BDS60 using the DACS™ SC plasticware and 42 were processed using 50 mL conical centrifuge tubes.

A total of 46 patients were infused with the BDS60-processed PBPC product; one patient withdrew before the transplant procedure. These 46 patients were evaluated for toxicity related to infusion of the BDS60-processed cells and for engraftment.

Assessment of infusional toxicity of BDS60-processed PBPC None of the patients experienced clinically significant changes in vital signs due to infusion of BDS60-prepared PBPC. Similarly, none of the patients had significant clinical or laboratory adverse events that were attributed to infusion of BDS60-processed PBPC. However, all patients experienced toxicity consistent with and attributed to myeloablative chemotherapy. Engraftment characteristics

The median time to neutrophil engraftment for both study subjects (45 evaluable; one patient died of sepsis on day 8 post PBPC infusion) and reference group was 9 days. The median times to platelet engraftment were 9 and 10 days, respectively.

There were no subjects in the study or reference group with delayed neutrophil engraftment. One patient each in the study group and the reference group experienced delayed platelet engraftment. Both of these subjects achieved platelet engraftment by post-transplant day 30. No patient in the clinical trial developed secondary graft failure. (Table 1).

TABLE 1. Engraftment Characteristics with BDS60-processed PBPC

	Study population n=46	Reference group n=12
CD34+ cells x 10^6 /kg infused		
Median	6.4	5.6
Range	(2.0-29)	(2.2-67)
Days to ANC > 500/mm^3		
Median	9	9
Range	(8-12)	(8-12)
Days to platelets >20,000/mm^3		
Median	9	10
Range	(7-19)	(7-25)

Device failures

There were no mechanical device failures in the clinical trial.

Efficacy for recovery of CD34+ cells

The data for recovery of CD34+ cells are presented in Table 2. The PBPC products were processed with BDS60 using three configurations of the separation container. Analysis indicated that performance results obtained with the first two device

configurations (prefilled 50 ml tubes and 50 ml tubes filled on-site) were not statistically significantly different. The results for both the 50 ml tube configurations were pooled; because there were differences in the performance of the DACS separation container configuration., as compared to the 50 ml tubes, the results for the tubes and DACS™ SC kit are presented separately. There were 17 apheresis products from 14 patients processed with the DACS™ SC kit and 42 apheresis products from 37 patients processed with 50 mL conical centrifuge tubes which contain a cell trap. The initial median TNC in PBPC processed with DACS™ SC was 2.1 x 10^{10} cells (range: 1.2 - 8.1) and for PBPC processed with 50 mL tubes was 2.1 x 10^{10} (range: 1.2 - 6.5). The median recovery of TNC was 32% (range 17 - 52%) after processing with the DACS™ SC kit and 42% (range 13 - 78%) after processing with the 50 mL tubes. Cell viability assessed by exclusion of Trypan Blue was greater than 90%.

TABLE 2. Percent Recovery of CD34 Positive Cells Processed with BDS60 According to Plasticware System

CD34+ cell recovery (%)	DACS™ SC n=17	Conical centrifuge tube n=42
Median	72%	79%
Range	(30-100%)	(34-100%)

After BDS60 processing, the ratio of CD34+ cells to TNC increased by nearly 2-fold (median 1.8 fold with DACS™ SC and 1.9 fold with conical tubes) as compared to the ratio of CD34+ cells to TNC in the initial PBPC product.

9.2 Supportive Studies

CD34+ cell recovery

Additional information regarding device performance data were generated in two additional, ongoing clinical studies. Study 1 was a single institution (Stanford University), phase 2 trial evaluating BDS60-processing of allogeneic PBPC. Data on device performance in 26 apheresis products obtained from 13 HLA-matched, related donors were submitted to the PMA. Study 2 was a single institution (M.D. Anderson Cancer Center), phase 2 trial evaluating BDS60-processing of allogeneic PBPC. Data on device performance in 9 PBPC products obtained from 7 normal donors was submitted to the PMA.

The data for recovery of CD34+ cells and total nucleated cells are presented in Table 3. The PBPC products were processed with BDS60 using 50mL centrifuge tubes that contain a silicone insert. The initial median total nucleated cells (TNC) in the PBPC

products was 5.7 x 10^{10} cells (range: 3.4–8.4) in Study 1 and 6.1 x 10^{10} cells (range: 4.7–7.4) in Study 2. The median recovery of TNC was 30.5% (range: 8.6–55.1) in Study 1 and 40.3% (range: 33.4–70.1) in Study 2. Cell viability assessed by Trypan Blue exclusion was 95% or greater after processing.

TABLE 3. Percent CD34 Cell Recovery

CD34+ Cell Recovery (%)	Study 1 (n=26)	Study 2 (n=9)
Median	71.4	88.7
Range	27.6–100	68.5–100

Reduction in CD34 negative cellular elements

The performance of BDS60 processing in reducing other cell populations, specifically total nucleated cells (TNC), red blood cells, neutrophils, platelets, lymphocytes, and monocytes, was evaluated in mobilized PBPC products from 11 individuals (3 normal donors and 8 with malignancies). All apheresis products were processed with BDS60 using the DACS^{TM}SC plasticware system. The median number of nucleated cells processed was 3.5 x 10^{10} (range 1.2-5.5). The results showed median CD34+ cell recovery of 77% (range: 31-96) with reduction of 37 to 87% in other starting cell populations (Table 4).

TABLE 4. Percent Reduction of CD34 Negative Cells With BDS60 (n=11)

Cell type	Median (%)	Range (%)
Total nucleated cells	71	48-91
RBC	87	69-97
Platelets	84	74-93
Neutrophils	82	67-93
Lymphocytes	81	64-91
Monocytes	37	22-90

10.0 CONCLUSIONS DRAWN FROM THE STUDIES

These data demonstrate that DACS^{TM}SC is effective for reducing the number and proportion of neutrophils, lymphocytes, monocytes, and platelets that are present in autologous, mobilized PBPC products. These cells are not required for hematopoietic reconstitution by PBPC after myeloablative therapy. The clinical trials conducted did not evaluate the clinical benefit of removing these cells. However, such cells may potentially contribute to adverse events associated with PBPC infusion. Some of the theoretical benefits of reduction of non-CD34+ cells include reduction in febrile reactions and reduction in cell clumping observed following neutrophil degranulation. In addition, the volume used in BDS60-cryopreserved products is reduced compared to the final volume of apheresis products that do not undergo additional processing. The clinical studies were not designed to evaluate whether the DMSO-related toxicities were reduced.

The principal safety consideration for DACS^{TM}SC and specifically for BDS60 is whether the device damages PBPC resulting in failure to engraft or in delayed engraftment. All 45 subjects evaluable for engraftment experienced rapid neutrophil engraftment. One subject experienced modestly delayed platelet engraftment. No patient experienced late (secondary) graft failure. This engraftment profile is similar to that observed in a small historical reference group who received unprocessed PBPC. A potential safety concern is that BDS60 makes PBPC intrinsically more toxic. There was no evidence of an increase in serious, infusion-related adverse events associated with infusion of BDS60-processed PBPC products.

Based on these considerations, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

11.0 PANEL RECOMMENDATIONS

No device panel was convened. The FDA relied on guidance from the Biological Response Modifiers Advisory Committee (BRMAC) regarding proposed and potential standards of approval for the safety and efficacy of PBPC selection devices which were addressed and discussed by the Committee in the May 1994 BRMAC meeting.

12.0 FDA DECISION

The sponsor's manufacturing facility was inspected on March 23, 1999 through April 13, 1999 and was found to be in compliance with the Device Good Manufacturing Practice regulations.

13.0 APPROVAL SPECIFICATIONS

Directions for use: See labeling (Attachment 1)

Hazards to Health from use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling (Attachment 1)

Post-approval Requirements and Restrictions: See approval order (Attachment 2)