

FDA Executive Summary

Prepared for the
February 26, 2016 Meeting of the
Gastroenterology-Urology Devices Panel

Classification of Centrifuge-Type Therapeutic
Apheresis Devices

Product Code:
LKN - Separator, automated, blood cell and plasma,
therapeutic

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1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the Gastroenterology-Urology Devices Advisory Panel (the Panel) for the purpose of securing recommendations regarding the classification of centrifuge-type therapeutic apheresis devices, a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of centrifuge-type therapeutic apheresis devices under product code “LKN.”

FDA is holding this panel meeting to obtain input on the risks to health and benefits of centrifuge-type therapeutic apheresis devices under product code “LKN.” The Panel will discuss whether these centrifuge-type devices should be classified into Class III (subject to General Controls and Premarket Approval), Class II (subject to General and Special Controls) or Class I (subject only to General Controls). If the Panel believes that classification into Class II is appropriate for these centrifuge-type devices under product code “LKN,” the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1. Current Regulatory Pathways

Centrifuge-type therapeutic apheresis devices under product code “LKN” are a pre-amendments, unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments of 1976, but was not classified by the original classification panels. Currently these devices are being regulated through the 510(k) pathway, and are cleared for marketing if their indications for use and technological characteristics are “substantially equivalent” to a legally marketed predicate device.

1.2. Device Description

Centrifuge-type therapeutic apheresis devices are designed to separate plasma or other blood components from whole blood, for the purposes of depletion or exchange of these components or plasma, and are regulated under product code “LKN” as “Separator, automated, blood cell and plasma, therapeutic.” Since these devices are unclassified, there is no regulation associated with the product code.

These devices are typically automated continuous-flow systems that are comprised of a blood component separator instrument that uses pumps, valves and sensors as well as a disposable apheresis kit, including an extracorporeal circuit, specific to the procedure being performed. The blood component separator draws whole blood from a patient, separates the blood into its components, utilizing centrifugal force as the basis of operation, collects one or more of the blood components, and returns the remainder of the blood components to the patient.

2. Regulatory History

Please refer to Table 1 and Table 2, below, for a listing of the manufacturers, device names, and associated 510(k) submission numbers for cleared centrifuge-type devices for therapeutic apheresis or plasma exchange under product code “LKN”:

Table 1: 510(k) Clearances for Centrifuge-Type Therapeutic Apheresis Devices

Device Name	Company Name	510(k)s	Clearance Date
Automated Blood Cell Separator	CRYOSAN, INC.	K830831	6/16/1983
Spectra Optia Apheresis System	TERUMO BCT,	K151368,	9/11/2015
		K141938,	3/23/2015
		K132429,	12/6/2013
		K131744,	8/9/2013
	<i>formerly owned by</i> CARIDIAN BCT,	K113480,	1/20/2012
		K103090,	11/19/2012
<i>formerly owned by</i> GAMBRO,	K071079,	8/2/2007	
<i>formerly known as the COBE</i> Spectra Blood Cell Separation System	<i>formerly owned by</i> COBE LABORATORIES,	K900105, K893962	3/22/1991 10/18/1989
<i>formerly known as the Automated</i> 8400 Blood Cell Separator	<i>formerly owned by IBM</i>	K831004,	9/12/1983
Fresenius COM.TEC Automated Blood Cell Separator Fresenius AS 104 Cell Separator	FRESENIUS	K060734,	9/1/2006
		K961706,	7/31/1996
		K895435	11/2/1990
MCS and MCS+ Systems and Therapeutic Plasma Exchange Set	HAEMONETICS CORP.	K953681	6/4/1996
Amicus Separator System	FENWAL, INC.	K141019,	6/10/2014
		K111702	3/22/2012

Table 2: 510(k) Clearances for Accessory Devices Used in Therapeutic Plasma Exchange

Device Name	Company Name	510(k)s	Clearance Date
Four Liter Bag For Use With Redy 2000 and Dialert Systems	ORGANON TEKNIKA CORP.	K874607	1/27/1988
Plasma Discard Bags	APHERESIS TECHNOLOGIES, INC.	K926409	3/02/1993

3. Indications for Use

The indications for use (IFU) statement identifies the condition and patient population for which a device should be appropriately used. Representative indications for use statements

for centrifuge-type therapeutic apheresis devices under product code “LKN” cleared in the 510(k)s noted in Table 1 are as follows:

- may be used to perform therapeutic plasma exchange (TPE) or plasma treatment.
- to remove plasma components and/or fluid.
- may be used to perform Red Blood Cell Exchange (RBCX) procedures for the transfusion management of Sickle Cell Disease in adults and children.

Historically, indications for use have also included the following more general indications:

- for use in apheresis procedures involving donors and patients.
- to harvest cellular components from the blood of certain patients where the attending physician feels the removal of such components may benefit the patient.

4. Clinical Background

This section summarizes the history of the use of automated blood cell separator devices (also known as apheresis devices) with an emphasis on centrifuge-type therapeutic apheresis devices under product code “LKN,” which are the focus of this classification panel.

4.1. Standard of Care

General Background

Apheresis is a form of extracorporeal therapy that involves removing whole blood from a donor or patient and separating out various components. Automated blood cell separation uses either centrifugal or filtration separation. Devices which utilize centrifugal separation are the focus of this classification panel. The circuit involves removal of whole blood from a donor or patient, separation of the blood into components, collection of one or more of those components, and finally, return of whole blood and certain components. There are two main forms of centrifugation: continuous flow centrifugation (CFC) in which whole blood is collected, spun, and returned simultaneously, and intermittent flow centrifugation (IFC), which works in cycles. While CFC may use one or two needles, IFC requires a single needle only.

The extracorporeal circuit volume varies (generally 250-500 mL). Other features of apheresis may include continual flow, rotating seal, anticoagulation control, substitution fluid control, hemolysis control and interface control. The system requires pumps and sensors and a comprehensive safety alarm system.

Types of Apheresis

Apheresis can be used for processing of blood for blood-banking purposes or processing of blood for therapeutic procedures. This classification process will only include a discussion of therapeutic apheresis (TA). There are many types of TA, and these are named based on the whole blood component which is removed. Plasmapheresis (PP) involves the removal of plasma and cytapheresis involves removal of cells.

Cytapheresis can involve the therapeutic removal of red blood cells (RBC) (erythrocytapheresis/RBC exchange), white blood cells (WBC) (leukopheresis), and platelets (thrombocytapheresis/plateletpheresis).

While PP includes separation and removal of plasma, a subset of PP which involves the replacement or exchange of the removed plasma is called therapeutic plasma exchange (TPE). In TPE, whole blood is removed from a patient and separated by a centrifuge into cells and plasma. The plasma is discarded while the cells, along with a substitution fluid, are returned to the patient. Erythrocytapheresis involves the separation of RBC from whole blood and is commonly employed for the treatment of diseases of the RBC such as sickle cell disease. Thrombocytapheresis is the collection of platelets in which RBCs, WBCs, and plasma are spared. Leukopheresis involves the removal of WBCs, including polymorphonuclear cells (neutrophils) or mononuclear cells. Based on a review of nearly 18,000 procedures at 70 hospitals and clinics (Kiproff DD *et al.*, 2001), PP/TPE is the most frequently performed TA procedure (95%) followed by leukopheresis (3%), thrombocytapheresis (1%), and erythrocytapheresis (1%).

Fluid replacement during apheresis

During apheresis, the system removes fluid (usually not more than 10 mL/kg body weight), which must be replaced to maintain intravascular volume. The type of “replacement fluid” varies and includes crystalloid (e.g., normal saline), serum albumin, fresh frozen plasma or another blood product. With each fluid, there are advantages and disadvantages, and the selection of fluid type may be dependent on patient age and size, disease, availability of fluids, and institutional practice.

Guidelines for Apheresis

The American Society for Apheresis publishes guidelines (Schwartz J *et al.*, 2013) for apheresis based upon a thorough literature review. The applicability of a therapy is based on a Category (I-IV) assignment. Simply, Category I denotes the recommendation of therapeutic apheresis for a particular condition as first line treatment, while Category II identifies apheresis as second line treatment. Categories III and IV identify apheresis as being not clearly established or ineffective/harmful, respectively. Category I indications (i.e., accepted first-line therapy) for TPE are included in the following table. Of note, many of these diseases are rare and are associated with high morbidity/mortality.

Table 3: Category I Indications for Therapeutic Plasma Exchange (TPE)

Speciality	Condition
Neurology	Acute Guillain–Barré syndrome
	Chronic inflammatory demyelinating polyneuropathy
	Myasthenia gravis
	Polyneuropathy associated with paraproteinaemias
	PANDAS ^a
Haematology	Thrombotic thrombocytopenic purpura
	Atypical haemolytic uraemic syndrome (autoantibody to factor H)
	Hyperviscosity syndromes (paraproteinaemias)
Renal	Severe/symptomatic cryoglobulinaemia
	Goodpasture’s syndrome (anti-glomerular basement membrane antibodies)
	Antineutrophil cytoplasmic antibody (ANCA)-associated rapidly progressive glomerulonephritis
	Recurrent focal segmental glomerular sclerosis
Metabolic	Antibody-mediated renal transplant rejection
	Familial hypercholesterolaemia (homozygous)
	Fulminant Wilson’s disease

^a Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.

From: Schwartz J et al., 2013

Other Category I indications for therapeutic apheresis using the centrifuge-type device include:

- Red Blood Cell (RBC) exchange - acute sickle cell disease (acute stroke), severe babesiosis
- Erythrocytapheresis - polycythemia vera, hereditary hemochromatosis,
- Leukocytapheresis - hyperleukocytosis with leukostasis.

Of note, thrombocytapheresis can also be performed with this device, and is described as a Category II indication for symptomatic thrombocytosis.

4.2. Risks

FDA has identified the following risks to health associated with centrifuge-type apheresis devices:

Table 4: Risks to Health Associated with Centrifuge-Type Apheresis Devices

Identified Risk	Description / Examples
Thrombosis in patient and device	This can include clotting of the extracorporeal circuit, vascular access clotting, or clotting of other blood vessels.
Adverse tissue reaction	This can result from the use of device components that are not biocompatible.

	This risk also includes allergic reactions, which can be reactions to device materials (e.g., reaction to ethylene oxide sterilant) or reactions to blood products used with the device.
Infection and pyrogen reactions	This risk includes febrile reactions, inflammatory response syndromes, infection, sepsis, and microbial contamination.
Device failure / disposable failure	This risk includes injury resulting from failure (e.g., electrical, mechanical, software) of one or more of the device components (e.g., reservoir leak/rupture, tubing separation/breakage)
Air embolism	This risk occurs if air enters the circuit and subsequently the bloodstream, which can result in occlusion of small blood vessels resulting in stroke, myocardial infarction, etc.
Hemolysis	This risk includes damage to red blood cells with subsequent release of cellular contents resulting from the mechanical processing of blood.
Blood loss/anemia	This risk includes blood leaks from the circuit, loss of blood from a discarded extracorporeal circuit after clotting, or increased risk of bleeding from anticoagulation medications or removal of clotting factors during therapy.
Toxic reaction to anticoagulant	This can include citrate toxicity, which is typically manifested by hypocalcemia (paresthesia, tetany, seizures, and cardiac arrhythmias) and alkalosis.
Electrical shock hazard	This risk can include electrical burns and cardiac arrhythmias.
Fluid imbalance	This risk can result in hypovolemia (e.g., hypotension, headache, nausea/vomiting, syncope) or fluid overload (e.g., hypertension, pulmonary congestion).
Inadequate separation of blood components	This risk involves the unintended removal of blood components (e.g., loss of immunoglobulins, drugs, electrolytes, coagulation factors, etc.).
Operator error	Incorrect use of the device can lead to additional clinical risks (e.g., data entry

	error that causes the system to incorrectly calculate patient total blood volume).
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The panel will be asked whether this list is a complete and accurate list of the risks to health presented by centrifuge-type devices under product code “LKN” (designed to separate plasma or blood components from whole blood) and whether any other risks should be included in the overall risk assessment of the device type.

5. Literature Survey

A search of the PubMed database was conducted on September 10, 2014 with the following search terms used to retrieve articles published in English since January 1, 1980 on apheresis devices: “Prosorba” OR “Fresenius AS104 Cell Separator” OR “Fresenius 2008K Dialysate Delivery System” OR “AMICUS Separator System” OR “Fresenius Tec automated cell separator” OR "SPECTRA Optia Apheresis System" OR "Gambro Plasmafiltration System" OR "Automated Blood Cell Separator" OR "COBE SPECTRA Blood Component Separator" OR “plasma centrifuge” OR "Plasma Filter" Or "Plasma Separation System" OR “therapeutic plasma exchange” OR “therapeutic plasma separator.”

The initial search resulted in 1,215 unique articles. Articles were selected for inclusion in the literature review for centrifuge devices cleared for market distribution in the U.S. which included reports of clinical studies conducted in humans to evaluate the effectiveness and safety of therapeutic apheresis (TA) procedures, regardless of the indications for use. Based on the review of the abstracts, 978 articles were excluded (520 non-clinical research, 176 case report, 135 non-English, 73 non-human, 40 sample size <10, 21 no endpoint, 12 non-systematic review or meta-analysis, 1 no abstract). The full texts of the remaining 237 articles were then reviewed. Based on this full text review, an additional 205 articles were excluded due to the following reasons: device not specified (69), device not approved in US (68), studies not specific on cleared device (28), studies not specific on device performance (22), non-systematic review (2), studies on Prosorba¹ device (10), and evaluated plasma membrane devices (6). This resulted in 32 articles on centrifuge devices that were included in this systematic literature review.

The detailed findings of this literature survey are provided as Appendix A. Based on this systematic literature review, the preponderance of the evidence indicates that a TA procedure with a centrifuge device is typically successful. The majority of reports were for TPE, which is the most frequently performed TA procedure using the centrifuge device. While there were few reports of the more rare therapies (leukopheresis, erythrocytapheresis, etc.), these are performed with the same centrifuge devices and have a similar adverse event (AE) profile. The AEs for this device-type are well-described and most of the AEs related with the use of centrifuge devices during TA procedures are non-serious and resolve without clinical consequences. As a result, FDA concludes that, for the centrifuges used for TA procedures

¹ The Prosorba column is regulated under premarket approval (PMA). The column contains Protein A covalently bound to an inert silica matrix, and is designed to process plasma and is used in conjunction with standard plasmapheresis equipment.

that are cleared for use in the US, there is a reasonable assurance of safety and effectiveness for treatment of patients with various disease indications.

6. Risks to Health Identified Using “Manufacturer and User Facility Device Experience” (MAUDE) Database

6.1. Overview of MAUDE Database

The MAUDE database is maintained by the Office of Surveillance and Biometrics at FDA. This database contains adverse events and reportable product problems with medical devices. The database was fully implemented in August 1996, and contains individual adverse event reports submitted by manufacturers, user facilities, importers, and voluntary reporters. Medical device manufacturers are required to report known adverse events as part of the general controls that most medical devices are subject to; Device users (e.g., patients, health care professionals, and other consumers are also encouraged to voluntarily report adverse events.

One does need to note the limitations to MDR reporting, including the fact that not all events are captured since there is a voluntary component to the reporting system. In addition, confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report.

6.2. MAUDE Search Results: Centrifuge-type Therapeutic Apheresis Devices

The FDA conducted queries of the MAUDE database on October 5, 2015 to identify any additional adverse events related to use of centrifuge-type therapeutic apheresis devices. Using the dates September 1, 2010 to August 31, 2015 and the device product code “LKN,” FDA completed a 5 year search of Medical Device Reports (MDRs) to assess the overall trend of Reports. The MDR categories are included in the table below:

Table 5: MDR Search Results (September 1, 2010 to August 31, 2015)

Dates of Search	Total MDRs	Deaths	Injury	Malfunction	Other / NA
Sep 2014 to Aug 2015	290	6	2	202	86
Sep 2013 to Aug 2014	130	5	3	0	102
Sep 2012 to Aug 2013	113	5	3	29	81
Sep 2011 to Aug 2012	489	4	2	329	156
Sep 2010 to Aug 2011	425	1	46*	107	271
* Of note, 40 of these 46 Injury Reports were from a single manufacturer and included language stating that the report was “being filed as a result of changes to our MDR eval process that were prompted by an FDA inspection.”					

To better understand the types of events that were reported, individual review of the MDRs was required. Due to the volume of reports, a detailed search of individual

MDRs was restricted to a sample from the most recent 12 months (from September 1, 2014 to August 31, 2015), except for death and injury reports, which were individually reviewed for the entire five year period. The 12-month sample of MDR narratives was used to inform and support the proposed Risks to Health. For additional details, please see Table 2 in Appendix B.

There were 56 injuries reported for the 5 year period (September 2010 to August 2015). As noted in Table 5 above, the majority of these reports were from a single manufacturer and included language stating that the reports were filed as a result of changes to their MDR evaluation process that were prompted by an FDA inspection. While these events were placed in the “Injury” category, they are largely indistinguishable from reported events categorized as “Malfunction” or “Other” in subsequent years. The review of the “Injury” MDR narratives was used to inform and support the proposed Risks to Health. For additional details, please see Table 3 in Appendix B.

There were 21 deaths reported for the 5 year period (September 2010 to August 2015). Of note, one of the MDR Death Reports described the death of a non-human primate, but this report was included for the sake of completeness. For the majority of the reports, the death was thought to be related to the patient’s underlying disease or condition and not the device. This is a reasonable assessment based on the available information as many of these patients were critically ill and undergoing treatment for life-threatening conditions in the intensive care unit setting. Additionally, based on the available information, the devices which underwent testing following the deaths demonstrated proper functionality. For additional details, please see the “Death” MDR narratives in Appendix B.

7. Summary

In light of the information available, the Panel will be asked to comment on whether centrifuge-type therapeutic apheresis devices under product code “LKN”:

meet the statutory definition of a Class III device:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and
- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury

or would be more appropriately regulated as Class II, in which:

- general and special controls, which may include performance standards, postmarket surveillance, patient registries and/or development of guidelines, are sufficient to provide reasonable assurance of safety and effectiveness;

or as Class I, in which

- the device is subject only to general controls, which include registration and listing, good manufacturing practices (GMPs), prohibition against adulteration and misbranding, and labeling devices according to FDA regulations.

For the purposes of classification, FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

7.1. Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified, and provide a reasonable assurance of the safety and effectiveness of centrifuge-type therapeutic apheresis devices under product code “LKN.” The following is a risk/mitigation table which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks:

Table 6: Risk/mitigation Recommendations for Centrifuge-Type Therapeutic Apheresis Devices under Product Code “LKN”

Identified Risk	Recommended Mitigation Measures
Thrombosis in patient and device	Performance testing Labeling Clinical performance testing
Adverse tissue reaction	Biocompatibility Sterility Expiration date testing Labeling
Infection and pyrogen reactions	Performance testing Sterility Expiration date testing Labeling
Device failure / Disposable failure	Performance testing Expiration date testing Labeling

Identified Risk	Recommended Mitigation Measures
Air embolism	Performance testing Labeling
Hemolysis	Performance testing Labeling
Blood loss/anemia	Performance testing Labeling
Toxic reaction to anticoagulant	Performance testing Labeling Clinical performance testing
Electrical shock hazard	Performance testing Labeling
Fluid imbalance	Performance testing Labeling Clinical performance testing
Inadequate separation of blood components	Performance testing Clinical performance testing
Operator error	Performance testing (usability) Labeling

Based on the recommended mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for the centrifuge-type devices under product code “LKN.” When evaluating the adequacy of the special controls, it is important to understand that the FDA assesses the ability of each special control identified to mitigate an identified risk to health.

Special Controls for Centrifuge-Type Apheresis Devices:

Based on these mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness of centrifuge-type apheresis devices:

- The patient-contacting components of the device must be demonstrated to be biocompatible;
- Performance data must demonstrate that the device performs as intended under anticipated conditions of use as follows:
 - functional testing must demonstrate:
 - mechanical integrity of the device and disposable;
 - device functionality in terms of separation and removal of blood components;
 - device functionality in terms of fluid and anticoagulation management when the device is used according to its labeling;
 - proper functionality of device safeguards and alarms;
 - mechanical hemolysis testing must be conducted;
 - a system-level hazard analysis must confirm that the device does not perform in an unexpected and/or unsafe manner;
 - software verification and validation testing must be performed;

- appropriate analysis and non-clinical testing must be conducted to validate electrical safety;
- appropriate analysis and non-clinical testing must be conducted to validate electromagnetic compatibility (EMC);
- performance data must demonstrate sterility of the device;
- performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life;
- Labeling must include the following:
 - a description of the device and individual device components; accessories that need to be used with the system, operational parameters, and software version;
 - a description of the pre-treatment, performance, and post-treatment steps needed to safely perform each therapy mode (if more than one may be performed);
 - a description of the alarms included in the system, the alarm format (e.g., visual, audible alarm), the suspected cause of the alarm condition, and how the user must respond to the alarm;
 - detailed instructions for the user to properly clean, disinfect, and maintain the device.
 - a detailed summary of the device-related and procedure-related complications pertinent to the use of the device;
 - a summary which describes the possible susceptibility to electromagnetic interference and possible electrical hazards associated with the use of the device; and
 - a troubleshooting guide for users to reference if problems are encountered
- Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and document any adverse events observed during clinical use.

If the panel believes that Class II is appropriate for centrifuge-type devices under product code “LKN,” the panel will be asked whether the identified special controls appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

7.2. Overview of Proposed Classification

Based on the identified risks to health and recommended mitigation measures, we recommend that centrifuge-type therapeutic apheresis devices under product code “LKN,” intended for use in therapeutic apheresis procedures, be regulated as Class II devices (special controls).

876.XXXX Centrifuge-Type Therapeutic Apheresis Device

- (a) *Identification.* A centrifuge-type therapeutic apheresis device is an automated blood cell and plasma separator intended for the therapeutic separation of blood components from whole blood using centrifugal separation principles for the purpose of depletion or exchange of cellular blood components or plasma in the treatment of various illnesses. During treatment, blood is withdrawn from the patient and circulated through an extracorporeal circuit and centrifuge chamber, enabling the removal of cellular blood components or plasma based on the density of these substances. The centrifuge-type therapeutic apheresis device is an

automated intermittent-flow or continuous-flow system that consists of the following devices:

- (1) The automated blood cell and plasma separator instrument consists of pumps, valves and sensors. It controls and monitors the parameters related to blood component processing, including the rate at which whole blood is pumped through the system, and the rate at which cellular blood components or plasma are removed from the patient. The automated blood cell and plasma separator draws whole blood from a patient, separates the blood into its components, utilizing centrifugal force as the basis of operation, removes one or more of the blood components, and returns the remainder of the blood components to the patient.
- (2) The therapeutic automated blood cell and plasma separator accessories include, but are not limited to the disposable apheresis kit, plasma discard bags, tubing lines and various treatment related monitors (e.g., pH, blood pressure, hematocrit, and blood recirculation monitors).

(b) *Classification.* Class II (special controls). The special controls for this device are:

- (1) The patient-contacting components of the device must be demonstrated to be biocompatible;
- (2) Performance data must demonstrate that the device performs as intended under anticipated conditions of use as follows:
 - (i) functional testing must demonstrate:
 - a. mechanical integrity of the device and disposable;
 - b. device functionality in terms of separation and removal of blood components;
 - c. device functionality in terms of fluid and anticoagulation management when the device is used according to its labeling;
 - d. proper functionality of device safeguards and alarms;
 - (ii) mechanical hemolysis testing must be conducted;
 - (iii) a system-level hazard analysis that confirms that the device does not perform in an unexpected and/or unsafe manner;
 - (iv) software verification and validation testing must be performed;
 - (v) appropriate analysis and non-clinical testing must be conducted to validate electrical safety;
 - (vi) appropriate analysis and non-clinical testing must be conducted to validate electromagnetic compatibility (EMC);
 - (vii) performance testing must demonstrate sterility of the device;
 - (viii) performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life;
- (3) Labeling must include the following:
 - (i) a description of the device and individual device components; accessories that need to be used with the system, operational parameters, and software version;

- (ii) a description of the pre-treatment, performance, and post-treatment steps needed to safely perform each therapy mode (if more than one may be performed);
 - (iii) a description of the alarms included in the system, the alarm format (e.g., visual, audible alarm), the suspected cause of the alarm condition, and how the user must respond to the alarm;
 - (iv) detailed instructions for the user to properly clean, disinfect, and maintain the device.
 - (v) a detailed summary of the device-related and procedure-related complications pertinent to the use of the device;
 - (vi) a summary which describes the possible susceptibility to electromagnetic interference and possible electrical hazards associated with the use of the device; and
 - (vii) a troubleshooting guide for users to reference if problems are encountered
- (4) Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use and document any adverse events observed during clinical use.

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of centrifuge-type therapeutic apheresis devices under product code “LKN” for use in therapeutic apheresis procedures.

8. References

Kiprof, D.D., et al., Adverse reactions associated with mobile therapeutic apheresis: analysis of 17,940 procedures. *J Clin Apher*, 2001. 16(3): p. 130-3.

Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, Szczepiorkowski ZM, Williams ME, Wu Y, Shaz BH. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. *J Clin Apher*. 2013 Jul;28(3):145-284.

Appendix A: Systematic Literature Review on Centrifuges Used in Therapeutic Apheresis (TA) Procedures

The objective of this systematic review of the literature is to summarize the safety and effectiveness of centrifuges cleared for market distribution in the United States, for use during therapeutic apheresis (TA) procedures. Of note, the term TA includes plasmapheresis (PP), therapeutic plasma exchange (TPE), leukopheresis, thrombocytapheresis/plateletpheresis, and erythrocytapheresis/red blood cell exchange.

A search of the PubMed database was conducted on September 10, 2014 with the following search terms used to retrieve articles published in English since January 1, 1980 on apheresis devices: “Prosorba” OR “Fresenius AS104 Cell Separator” OR “Fresenius 2008K Dialysate Delivery System” OR “AMICUS Separator System” OR “Fresenius Tec automated cell separator” OR “SPECTRA Optia Apheresis System” OR “Gambro Plasmafiltration System” OR “Automated Blood Cell Separator” OR “COBE SPECTRA Blood Component Separator” OR “plasma centrifuge” OR “Plasma Filter” Or “Plasma Separation System” OR “therapeutic plasma exchange” OR “therapeutic plasma separator.” While the search did not include specific terms for the more rarely performed therapies (leukopheresis, thrombocytaphereis, erythrocytapheresis), the search did include search terms for all currently marketed centrifuge devices used for TA.

The initial search resulted in 1,215 unique articles. Articles were selected for inclusion in the literature review if reporting on clinical studies conducted in humans to evaluate the effectiveness and safety of TA procedures using centrifuge devices cleared for market distribution in the U.S., regardless of the indication for use. Based on the review of the abstracts, 978 articles were excluded (520 non-clinical research, 176 case report, 135 non-English, 73 non-human, 40 sample size <10, 21 no endpoint, 12 non-systematic review or meta-analysis, 1 no abstract). The full texts of the remaining 237 articles were then reviewed. Based on this full text review, an additional 205 articles were excluded due to the following reasons: device not specified (69), device not approved in US (68), studies not specific on approved device (28), studies not specific on device performance (22), non-systematic review (2), studies on Prosorba² device (10), and evaluated plasma membrane devices (6). This resulted on 32 articles on centrifuge devices that were included in this systematic literature review.

Overview of the studies included in the systematic review of the literature

The 32 articles selected for inclusion in the systematic review were published between 1996 and 2014, with 17 of the studies conducted in US, 13 conducted in Europe and one study each conducted in Korea and Australia. There were 24 single arm studies, 15 of which were retrospective and 9 prospective. Three randomized controlled trials (RCTs) compared a TA group with a control group (not treated with the rheohaemapheresis procedures), and 5 other studies compared two different centrifuge devices. The information of mean or median age of patients enrolled in the study was available from 21 studies. Two studies enrolled only pediatric patients with a mean age of 2.78 years old (range from 0.75 to 14 years) and 7 years old (range from 0.97 to 7.06 years), and

² The Prosorba column is regulated under premarket approval (PMA). The column contains Protein A covalently bound to an inert silica matrix, and is designed to process plasma and is used in conjunction with standard plasmapheresis equipment.

the rest of the studies had a mean or median age of 34-66 years old. Gender information was available from 19 studies, 264 (53.1%) of the enrolled patients from these studies were males and 233 (46.9%) were females. TA procedures were used for patients diagnosed with various hematologic, neurologic, nephrologic, and rheumatologic disorders; acute pancreatitis; age-related macular degeneration; and cancer. In 26 studies, COBE Spectra were used with TA, which represents the most frequently studied centrifuge device. Other devices studied were the Spectra Optia and the Fresenius, in 5 and 6 studies each. AMICUS cell separator systems were studied in two studies. There were 18 articles that included information on both effectiveness and safety, 8 articles on effectiveness only and 6 articles that included information on safety only.

Summary of Effectiveness in Non-Comparative Studies

Effectiveness was defined in different ways because there are several different indications and each indication may have one or more parameters to assess it such as: rates or percentages of disease improvement (defined in different ways for each indication), remission of the condition, reduction of the incidence rate of relapses, and desired or normal blood laboratory level results indicating that the expected response was achieved. The clinical indications for which the device was used included in this section are as follows: Myasthenia Gravis^[1-4], Age-Related Macular Degeneration^[5,6], Acute Pancreatitis^[7], Neuroblastoma, Brain Tumor, Ewing Sarcoma^[8], ABO-Major-Mismatched Bone Marrow Transplantation^[9], End-Stage Renal Disease Receiving ABO-Incompatible Renal Transplantation^[10-12], Intermediate Syndrome (IMS) Due to Organophosphate (OP) Intoxication^[13], Pediatric Sepsis-Induced Acute Multi-System Organ Failure^[14], Pediatric Stem Cell Transplant-Associated Thrombotic Microangiopathy with multiorgan failure^[15] Recipient of ABO Incompatible Living Donor Liver Transplantation^[16], Heart Transplant Presumed Antibody-Mediated^[17], Breast Cancer, Multiple Myeloma, non-Hodgkin Lymphoma, Acute Leukemia, Chronic Lymphocytic Leukemia, Hodgkin Lymphoma, and Amyloidosis^[18], Thrombotic Thrombocytopenic Purpura, Multiple Myeloma, Hemolysis Elevated Liver Enzymes Low Platelet Count, and Snake Bite^[19], Thyrotoxicosis^[20], Multiple Sclerosis^[3,21], and Thrombotic Thrombocytopenic Purpura^[22].

After reviewing the evidence for effectiveness reported in 22 non-comparative studies, we found there were various levels of effectiveness when centrifuges were used for the clinical indications mentioned above. Effectiveness ranged from 34% (i.e., hematopoietic recovery of nucleated cells in ABO-major-mismatched bone marrow transplantation)^[16] to 100% (e.g., patients survival (10/10)^[10], complete remission was achieved for acquired thrombotic thrombocytopenic purpura (15/15), snake bites (5/5), hemolysis elevated liver enzymes and low platelet count (14/14), and multiple myeloma (10/10))^[8,15].

Patients with myasthenia gravis showed clinical improvement, weaned off medications, improvement of the median Hughes score, and reduction of the median time to achieve response with an overall 82% effectiveness^[3]. For the same indication, Collard et al.^[4] found the device to be effective when measuring the magnitude of serum cholinesterase reduction after treatment as compared to baseline ($p < 0.001$).

Blaha et al.^[5,6] reported for non-vascular form of age-related macular degeneration (AMD), that among treated patients, best-corrected visual acuity (BCVA) increased substantially from 0.61 (range: 0.06 - 1.00) to 0.68 (range: 0.35 - 1.00) after 2.5 years ($p = 0.035$). No substantial changes

or differences in scotopic activity were found, whereas cone response and paramacular activity in the more peripheral region between 14° and 22° of eccentricity were significantly higher in treated patients.

In patients receiving ABO-Major-Mismatched Bone Marrow Transplantation (BMT), the use of the device for TA treatment was related to hematopoietic recovery as follows: nucleated cells (33.7%), granulocytes (49%), CD3+ cells (82%), CD34+ cells (82%), and circulating granulocyte/macrophage progenitor cells (93.3%)^[16]. For patients with ABO incompatible living donor liver transplantation, Kim et al.^[16] found the device to be effective as indicated by an increase in graft survival, and the reduction of IgM and IgG titers. Patient and graft survival was 100% and there was no acute humoral rejection in recipients at a 10 months mean follow-up. For TPE treated patients with heart transplant presumed antibody-mediated rejection, the correlation between predicted and real CD34+ cells in leukopheresis collections was indicative of rapid improvement in allograft function and device's effectiveness^[17]. The proportion of episodes with normal left ventricular ejection fraction or LVEF ($\geq 55\%$) at baseline was only 28%, compared with 68% following the course of TA^[17]. Erkurt et al.^[19] found the device to be effective in reestablishing improved-normal levels of platelet counts, total protein levels, and LDL levels in patients with thrombotic thrombocytopenic purpura (TTP), multiple myeloma, hemolysis elevated liver enzymes low platelet count, and snake bite. In this Erkurt et al. study, complete remission of disease/condition was achieved on 13 patients (87%) in primarily TTP, and in all patients in the other three diseases.

Graspa et al.^[21] published that when treating multiple sclerosis, the expanded disability status scale showed recovery, no relapses occurred during treatment, spasticity improved in all patients, and one patient with cerebellar tremor was free of it after 6 months of therapy.

O'Brien et al.^[22] found an increase in remission and reduction of disease's relapse when the device was used in patients of acquired thrombotic thrombocytopenic purpura treated with apheresis. Ninety percent of patients responded to TPE as shown in the improvement of blood laboratory results and disease remission.

Qu et al.^[14] reported the use of TPE with COBE Spectra on 11 previously healthy children who developed acute multi-system organ failure (MSOF) associated with fulminant bacterial infections. The only death occurred in a patient who died the same day after his first TPE treatment which was initiated 24 hours after the development of the MSOF. Normalization of platelet count was achieved at day 2–4 in all 10 patients who were alive. Initial organ function improvements occurred in most patients with 2–4 TPE treatments. All 10 patients who were alive at 30 days had long term (≥ 1 year) survival.

Sivakumaran et al.^[10] and Tobian et al.^[12] reported allograft and patient survival after TPE with COBE Spectra in patients with end-stage renal disease that receiving ABO-incompatible renal transplantation. In the Sivakumaran Study, 9 of 10 allografts were functioning properly at study closure and no patient deaths were observed. In the Tobian Study, the one-year death-censored graft survival is 100% and patient survival is 97.6%.

The study by Yilmaz et al.^[13] found that 13 (76.5%) patients with intermediate syndrome (IMS)

due to organophosphate (OP) intoxication showed clinical improvement and were discharged after the TPE process.

Assessment of Effectiveness and Critique for Non-Comparative Studies

Our systematic review of the literature shows that the apheresis devices (centrifuges) were used for several clinical indications and the effectiveness was measured in different ways per study and according to the specific clinical indication. Although, several clinical indications have been evaluated, only one or two study publications were found for each clinical indication. Therefore, it is hard to draw definitive conclusions on how effective these devices are for each clinical indication. None of the included articles reported lack of or negative effectiveness. However, most of the publications were single cohort retrospective studies without a comparison or control group. Only one RCT was published for age-related macular degeneration, which indicated a successful use of the device and a high degree of treatment effectiveness^[5,6]. Most of the studies were conducted with small samples of patients and the follow-up time was short (typically from a few days to one year). Furthermore, publication bias cannot be ruled out as the reason why not a single study reported lack of effectiveness in this literature review. In spite of the limitations found in the published articles, the overall assessment is that these centrifuge-based devices are effective when used for TPE procedures.

Summary of Safety in Non-Comparative Studies

The safety of the centrifuges used in TA procedures was evaluated based on the incidence of adverse events (AE) and/or complications, side effects and death. The clinical indications for device use are the same as stated in the above effectiveness section.

The rates of adverse events were reported per number of procedures or per number of patients. Rates of AE varied significantly across the studies, with AE rates of 3.9%^[23], 5.3%^[19], 5.74%^[5,6], 15.4%^[9,11], 26.1%^[22], and 36%^[27], representing various time frame and types of adverse events. Most of these events were Grade-I (Mild) or II (Moderate) and resolved without treatment. The most commonly reported AEs were hypotension, allergic reactions, nausea- vomiting, paresthesia, and arrhythmias. Many of the AEs were parasympathetic reactions to treatment (e.g., vasovagal disturbances). Infection, bleeding, abnormalities in blood counts, electrolyte changes, and injuries to specific organ were rarely reported. Erkurt et al.^[19] estimated that an AE may be seen in 3–20% of TPE procedures. No AEs were reported in Qu et al.^[14] and Sivakumaran et al.^[10] studies.

Mortality was rarely studied as a device-specific study outcome due to the clinical indication for which the patients were treated. Abdel-Rahman et al.^[24] and Hayes et al.^[25] studied groups of subjects that were treated with centrifuges in TPE procedures. Both studies compared patients who died and survived and found that older patients are associated with a high death rate but still, the reason could be multifactorial and no association of the high mortality rate with the device or procedure can be determined. Erkurt et al.^[19] estimated the overall mortality rate in TPE to be 1–3 per 10,000 procedures.

Assessment of Safety and Critique for Non-Comparative Studies

Our systematic review of the literature shows that apheresis devices and procedures are safe. The majority of the articles focused on device effectiveness, and even when device safety was used as a study outcome, such as mortality, because the underlying health conditions were so serious, the results were equivalent to evaluating the device effectiveness in slowing down the progression of the underlying condition, and preventing death. The device safety concerns are mainly reactions to the procedure, including vasovagal disturbances that are generally transient, although in some cases termination of the procedure was necessary. Incidence of death was rarely reported and causation relative to the device could not be determined.

Many of the papers share some common limitations in the study design - retrospective, small sample size, no control, and lack of follow-up information or no long term follow-up. Additionally, many of the articles focus on the TA procedures and do not include device specific information.

Summary of Comparative Studies

There were five studies comparing effectiveness and/or safety outcomes of COBE Spectra with a few other US approved centrifuge devices used for TPE procedures. Four studies were conducted in US and one in France.

Effectiveness

In the comparative studies, primary effectiveness was defined as plasma removal efficiency (PRE) (%). The indications covered in these comparative studies included various hematologic, neurologic, nephrologic, and rheumatologic disorders.

Four studies^[28-31] compared effectiveness outcomes of COBE Spectra with that of Spectra Optia, Fresenius AS104 or AMICUS separator system in randomized or non-randomized prospective paired trials. A total of 17 to 30 patients were enrolled in each of the studies. In all studies, PRE was better for other centrifuge devices (79.5%-90.0%) than that of COBE Spectra (69.0%-79.3%). In two randomized trials^[30, 31] PRE for AMICUS or Spectra Optia was superior to that of COBE Spectra. In another randomized trial^[28] the Fresenius AS104 cell separator had significant higher PRE than that of COBE Spectra. In the non-randomized prospective study^[29], the PRE was not significantly different between Spectra Optia and COBE Spectra, but the PRE- anticoagulant corrected values were significantly higher in Spectra Optia than in COBE Spectra. Although the PRE in COBE Spectra was lower than other studied centrifuge devices, the device is generally considered effective in plasma removal with TPE^[1, 4-7, 9, 16, 20, 22].

In addition to PRE, two randomized trials^[30, 31] also demonstrated significantly higher fluid balance accuracy as a secondary effectiveness endpoint in other centrifuge devices compared to that of the COBE Spectra, but the difference in fluid balance accuracy was not clinically significant.

Safety

In the comparative studies, the safety of centrifuges used in TA procedures was evaluated based on the occurrence of AEs and/or SAEs during the procedures. The indications covered in these

comparative studies included various hematologic, neurologic, nephrologic, and rheumatologic disorders.

The adverse events related with the use of centrifuge devices were assessed in all of the five studies [28-32]. Two of the four randomized or non-randomized prospective paired trials reported no AEs [29] or SAEs [30]. The remaining two prospective paired trials reported a few adverse events during the studies. In the study by Winters et al. [31], four patients reported 7 AEs during AMICUS procedures (n=35) and four patients reported 5 AEs during COBE Spectra procedures (n=35). Three events were reported as possibly related to the TA procedure including nausea and headache reported by one patient during an AMICUS procedure and fatigue reported by one patient during the COBE Spectra procedure. There were no serious AEs reported for either device. No device malfunctions were reported. In the study by Burgstaler et al. [28], AEs were only seen in 3 of 40 procedures (8%) and were minor. One patient with Guillain Barre Syndrome experienced paresthesia of the face while on the COBE Spectra. The patient responded to the administration of 5ml 10% calcium gluconate and completed the procedure without further incident. Another patient with myasthenia gravis experienced hypotension while on COBE Spectra and Fresenius AS104 cell separator. The patient responded to the administration of normal saline.

Bachier et al. [32] retrospectively analyzed 159 adult patients underwent infusion of autologous peripheral blood stem cells (PBSC) on either the COBE Spectra (N=85) or Fresenius AS104 cell separator (N=74). No serious adverse events occurred during PBSC infusion except that 3 of 159 patients experienced seizures during infusion of PBSC and all 3 were treated using the COBE Spectra. It was also reported that high WBC concentrations in the PBSC product before freezing in patients on COBE Spectra is associated with the occurrence of seizure. The authors further conducted a prospective study to follow 80 infusion procedures in 65 patients using the COBE Spectra (n=65) or the Fresenius AS104 (n=15). Products with mid-collection WBC concentration greater than 450 ± 103 /mL were identified, and additional autologous plasma was collected at the time of collections so that the final product could be diluted before cryopreservation. No SAEs were observed in either device group.

Assessment and Critique of Comparative Studies

The data from comparative studies indicate that some centrifuge devices are more effective in plasma removal efficiency as compared to that of COBE Spectra. The devices are safe with a low risk of non-serious adverse events occurred during the procedure and no AEs reported post-procedure. There is no particular safety concern on any cleared centrifuge device except in one study, a low incidence of seizure was observed due to high WBC concentration in the PBSC product before freezing in patients on COBE Spectra during infusion of PBSC. No seizures were observed when the PBSC product was diluted in a subsequent prospective study.

The interpretation of the results from the comparative studies in this review is limited by small sample size and short follow-up time due to crossover study design.

Overall Conclusions

Based on this systematic literature review, the preponderance of the evidence indicates that a TA procedure with a centrifuge device is typically successful. The majority of reports were for TPE, which is the most frequently performed TA procedure using the centrifuge device. While there were few reports of the more rare therapies (leukopheresis, erythrocytapheresis, etc.), these are performed with the same centrifuge devices and have a similar AE profile. The AEs for this device-type are well-described and most of the AEs related with the use of centrifuge devices during TA procedures are non-serious and resolve without clinical consequences. As a result, FDA concludes that, for the centrifuges used for TA procedures that are cleared for use in the US, there is a reasonable assurance of safety and effectiveness for treatment of patients with various disease indications.

References

1. Triantafyllou, N.I., et al., *Periodic therapeutic plasma exchange in patients with moderate to severe chronic myasthenia gravis non-responsive to immunosuppressive agents: an eight year follow-up*. Ther Apher Dial, 2009. **13**(3): p. 174-8.
2. Guptill, J.T., et al., *A retrospective study of complications of therapeutic plasma exchange in myasthenia*. Muscle Nerve, 2013. **47**(2): p. 170-6.
3. Kaynar, L., et al., *Therapeutic plasma exchange in patients with neurologic diseases: retrospective multicenter study*. Transfus Apher Sci, 2008. **38**(2): p. 109-15.
4. Collard, C.D., et al., *Cumulative reduction in serum cholinesterase following repeated therapeutic plasma exchange*. J Clin Anesth, 1996. **8**(1): p. 44-8.
5. Blaha, M., et al., *The importance of rheological parameters in the therapy of the dry form of age-related macular degeneration with rheohaemapheresis*. Clin Hemorheol Microcirc, 2012. **50**(4): p. 245-55.
6. Blaha, M., et al., *Rheohaemapheresis in the treatment of nonvascular age-related macular degeneration*. Atheroscler Suppl, 2013. **14**(1): p. 179-84.
7. Stefanutti, C., et al., *Therapeutic plasma exchange in patients with severe hypertriglyceridemia: a multicenter study*. Artif Organs, 2009. **33**(12): p. 1096-102.
8. Witt, V., et al., *Performance of a new separator system for routine autologous hematopoietic progenitor cell collection in small children*. J Clin Apher, 2007. **22**(6): p. 306-13.
9. Larghero, J., et al., *ABO-mismatched marrow processing for transplantation: results of 114 procedures and analysis of immediate adverse events and hematopoietic recovery*. Transfusion, 2006. **46**(3): p. 398-402.
10. Sivakumaran, P., et al., *Therapeutic plasma exchange for desensitization prior to transplantation in ABO-incompatible renal allografts*. J Clin Apher, 2009. **24**(4): p. 155-60.
11. Tobian, A.A., et al., *Therapeutic plasma exchange reduces ABO titers to permit ABO-incompatible renal transplantation*. Transfusion, 2009. **49**(6): p. 1248-54.
12. Tobian, A.A., et al., *The critical role of plasmapheresis in ABO-incompatible renal transplantation*. Transfusion, 2008. **48**(11): p. 2453-60.
13. Yilmaz, M., et al., *Effectiveness of therapeutic plasma exchange in patients with intermediate syndrome due to organophosphate intoxication*. Am J Emerg Med, 2013. **31**(6): p. 953-7.

14. Qu, L., et al., *Outcomes of previously healthy pediatric patients with fulminant sepsis-induced multisystem organ failure receiving therapeutic plasma exchange*. J Clin Apher, 2011. **26**(4): p. 208-13.
15. Jodele, S., et al., *Does early initiation of therapeutic plasma exchange improve outcome in pediatric stem cell transplant-associated thrombotic microangiopathy?* Transfusion, 2013. **53**(3): p. 661-7.
16. Kim, J.M., et al., *ABO-incompatible living donor liver transplantation is suitable in patients without ABO-matched donor*. J Hepatol, 2013. **59**(6): p. 1215-22.
17. Singh, N., et al., *Therapeutic plasma exchange rapidly improves cardiac allograft function in patients with presumed antibody-mediated rejection*. J Clin Apher, 2014.
18. Del Fante, C., et al., *Clinical impact of a new automated system employed for peripheral blood stem cell collection*. J Clin Apher, 2006. **21**(4): p. 227-32.
19. Erkurt, M.A., et al., *Therapeutic plasma-exchange in hematologic disease: results from a single center in Eastern Anatolia*. Transfus Apher Sci, 2013. **48**(3): p. 335-9.
20. Ezer, A., et al., *Preoperative therapeutic plasma exchange in patients with thyrotoxicosis*. J Clin Apher, 2009. **24**(3): p. 111-4.
21. Grapsa, E., et al., *Therapeutic plasma exchange combined with immunomodulating agents in secondary progressive multiple sclerosis patients*. Ther Apher Dial, 2008. **12**(2): p. 105-8.
22. O'Brien, K.L., et al., *The use of 50% albumin/plasma replacement fluid in therapeutic plasma exchange for thrombotic thrombocytopenic purpura*. J Clin Apher, 2013. **28**(6): p. 416-21.
23. Kiprof, D.D., et al., *Adverse reactions associated with mobile therapeutic apheresis: analysis of 17,940 procedures*. J Clin Apher, 2001. **16**(3): p. 130-3.
24. Abdel-Rahman, E.M., J. Hayes, and R.A. Balogun, *Therapeutic plasma exchange in the elderly: experience at a tertiary center*. J Clin Apher, 2012. **27**(3): p. 108-11.
25. Hayes, J.S., et al., *Therapeutic plasma exchange for renal-related conditions in the elderly: ten years experience in one center*. Semin Dial, 2012. **25**(2): p. 159-64.
26. Blaha, M., et al., *The importance of rheological parameters in the therapy of microcirculatory disorders*. Clin Hemorheol Microcirc, 2009. **42**(1): p. 37-46.
27. Shemin, D., D. Briggs, and M. Greenan, *Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures*. J Clin Apher, 2007. **22**(5): p. 270-6.
28. Burgstaler, E.A. and A.A. Pineda, *Therapeutic plasma exchange: a paired comparison of Fresenius AS104 vs. COBE Spectra*. J Clin Apher, 2001. **16**(2): p. 61-6.
29. Hequet, O., et al., *Comparison of plasma exchange performances between Spectra Optia and COBE Spectra apheresis systems in repeated procedures considering variability and using specific statistical models*. Transfus Apher Sci, 2014. **51**(1): p. 47-53.
30. Tormey, C.A., et al., *Improved plasma removal efficiency for therapeutic plasma exchange using a new apheresis platform*. Transfusion, 2010. **50**(2): p. 471-7.
31. Winters, J.L., et al., *A multicenter evaluation of a new therapeutic plasma exchange procedure*. Transfusion, 2013. **53**(12): p. 3269-78.
32. Bachier, C., et al., *High white blood cell concentration in the peripheral blood stem cell product can induce seizures during infusion of autologous peripheral blood stem cells*. Biol Blood Marrow Transplant, 2012. **18**(7): p. 1055-60.

Appendix B: Public MAUDE Information on Centrifuge-Type Therapeutic Apheresis Devices, product code “LKN,” Medical Device Reports (MDRs)

Overview of MAUDE Database

The MAUDE database is maintained by the Office of Surveillance and Biometrics at FDA. This database contains adverse events and reportable product problems with medical devices. The database was fully implemented in August 1996, and contains individual adverse event reports submitted by manufacturers, user facilities, importers, and voluntary reporters. Medical device manufacturers are required to report known adverse events as part of the general controls that most medical devices are subject to; Device users (e.g., patients, health care professionals, and other consumers who are also encouraged to voluntarily report adverse events).

One does need to note the limitations to MDR reporting, including the fact that not all events are captured since there is a voluntary component to the reporting system. In addition, confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report.

MAUDE Search Results: LKN

The FDA conducted queries of the MAUDE database on October 5, 2015 to identify adverse events related to use of LKN. Using the dates September 1, 2010 to August 31, 2015 and the device product code “LKN,” FDA completed a 5 year search of Medical Device Reports (MDRs) to assess the overall trend of Reports. The MDR categories are included in the table below:

Table 1: MDR Search Results (September 1, 2010-August 31, 2015)

Dates of Search	Total MDRs	Deaths	Injury	Malfunction	Other / NA
Sep 2014 to Aug 2015	290	6	2	202	86
Sep 2013 to Aug 2014	130	5	3	0	102
Sep 2012 to Aug 2013	113	5	3	29	81
Sep 2011 to Aug 2012	489	4	2	329	156
Sep 2010 to Aug 2011	425	1	46*	107	271
* Of note, 40 of these 46 Injury Reports were from a single manufacturer and included language stating that the report was “being filed as a result of changes to our MDR eval process that were prompted by an FDA inspection.”					

To better understand the types of events that were reported, individual review of the MDRs was required. Due to the volume of reports, a detailed search of individual MDRs was restricted to a sample from the most recent 12 months (from September 1, 2014 to August 31, 2015), except for deaths and injuries, which were individually reviewed for the entire five year period (see below). Of note, several of the MDRs were reported for blood donation procedures (including mononuclear cell collection), which are outside the

scope of the LKN classification as these device functions are regulated by the FDA Center for Biologics Evaluation and Research (CBER). They were included for the sake of completeness.

Total MDR Sample (September 1, 2014 to August 31, 2015)

Using these dates, the query returned 290 Medical Device Reports (MDRs). After reviewing the individual MDR reports, the reported adverse events were grouped into the following risk categories (please note that multiple adverse events may be related to a single MDR):

Table 2: Risk Categories from MDR Sample (September 1, 2014-August 31, 2015)

Number (%)	Risk Category	Specific Examples
203 (70)	Use error	Data entry error* (196) Improper clamping of lines (7)
20 (6.9)	Device/pump Failure	Centrifuge fluid leaks (13) Electrical failure (5) Touchscreen failure (1) Abnormal noise (1)
17 (5.9)	Inadequate fluid balance	Fluid balance alarm (12) Increased hematocrit (3) Syncope (2)
13 (4.5)	Treatment interruption/termination	Air Detection (10) Hemolysis (3)**
9 (3.1)	Disposable failure	Separation Breakage Tubing leaks Expired kit component (1)
7 (2.4)	Inadequate separation of cells/plasma	Inadequate yield during harvest (5) Cells detected in plasma line (2)
5 (1.7)	Blood loss	Blood leak Clotted circuit Platelet depletion during harvest
5 (1.7)	Allergic reaction	Sterilant (EtO) reaction (3) Transfusion reaction (2)
4 (1.4)	Thrombosis	Blood clots in tubing
2 (0.7)	Hypocalcemia	Tetany, bronchospasm
1 (0.3)	Febrile reaction	Fever, tachycardia
<p>*Multiple (n=194) reports of customer incorrectly entering the patient's height and weight for various procedures (therapeutic plasma exchange, white blood cell collection, or red blood cell exchange). The company issued a Safety Notification to all of their customers and submitted an updated software version (v11.3) to fix the issue, which was cleared by FDA in a subsequent 510(k) submission (K153601).</p> <p>**Device alarms detected hemolysis, which was thought to be associated with underlying condition in all cases (e.g., hemolytic anemia in TTP).</p>		

This 12-month sample of individual MDR narratives was used to inform and support the proposed Risks to Health.

Injuries

There were 56 injuries reported for the 5 year period (September 2010 to August 2015). As noted in Table 1 above, the majority of these reports were from a single manufacturer and included language stating that the reports were filed as a result of changes to their MDR evaluation process that were prompted by an FDA inspection. While these events were placed in the “Injury” category, they are largely indistinguishable from reported events categorized as “Malfunction” or “Other” in subsequent years. After reviewing the individual MDR reports, the reported adverse events were grouped into the following risk categories:

Table 3: Risk Categories for “Injury” MDRs (September 1, 2010-August 31, 2015)

Number (%)	Risk Category	Specific Examples
12 (21.4)	Toxic reaction to anticoagulant	Citrate reaction / hypocalcemia symptoms; arrhythmia (1); seizure (1)
12 (21.4)	Fluid imbalance	Hypervolemia/ hypovolemia (5); hypotension (4); syncope (3)
7 (12.5)	Adverse tissue reaction	Symptoms (hives, dyspnea); reported allergic reaction to albumin replacement fluid, ethylene oxide sterilant, blood products, etc.
7 (12.5)	Blood loss/anemia	Blood loss from clotted circuit; blood leaks
5 (8.9)	Thrombosis in patient and device	Phlebitis of vascular access site (2); deep venous thrombosis (1); arterial thrombosis (1); myocardial infarction (1)
5 (8.9)	Hemolysis	Hemolysis from underlying disease (e.g., TTP); transfusion reaction; administration of hypotonic replacement fluids
2 (3.6)	Air embolism	Air observed in tubing resulting in treatment interruption
2 (3.6)	Infection and pyrogen reactions	Sepsis from contaminated blood products (1); operator needle stick injury (1)
3 (5.4)	No apparent injury	No patient injury noted in MDR Report
1 (1.8)	Electrical shock hazard	Operator experienced electrical burn

The review of the individual “Injury” MDR narratives was used to inform and support the proposed Risks to Health.

Deaths

There were 21 deaths reported for the 5 year period (September 2010 to August 2015). Of note, one of the MDR Death Reports described the death of a non-human primate, but this report was included for the sake of completeness. For the majority of the reports, the death was thought to be related to the patient's underlying disease or condition and not the device. This is a reasonable assessment based on the available information as many of these patients were critically ill and undergoing treatment for life-threatening conditions in the intensive care unit setting. Additionally, based on the available information, the devices which underwent testing following the deaths demonstrated proper functionality. For additional details, please see the full MDR reports for each death, which are included below:

2014-2015

Death#1 (Report#1722028-2015-00225)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT WAS ADMITTED TO THE ICU. THE PHYSICIAN CONFIRMED THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) WAS CONFIRMED AND AN EMERGENCY THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE WAS PLANNED. DURING THE INSERTION OF A JUGULAR LINE INTO THE PATIENT; THE PATIENT WENT INTO CARDIAC ARREST. THE HOSPITAL REVIVED THE PATIENT AND PLACED A SUBSEQUENT LINE IN THE FEMORAL ARTERY AND THE TPE COMMENCED. APPROXIMATELY 2 MINUTES INTO THE PROCEDURE; THEY RECEIVED SEVERAL RBC DETECTOR ALARMS AND A'CELLS DETECTED IN PLASMA LINE' ALARM. THE OPERATOR PAUSED THE PROCEDURE AND CHECKED THE SETUP OF THE DISPOSABLE SET WITH NO ISSUES FOUND. THE OPERATOR THEN NOTICED THE FLUID IN THE PLASMA LINE WAS RED IN COLOR. WHILE THE OPERATOR CONTINUED THE PROCEDURE AND REDUCED THE INLET FLOW RATE AND HEMATOCRIT LEVEL WITH NO EFFECT; THE OPERATOR ENDED THE PROCEDURE AND DISCONNECTED THE PATIENT WITH PLANS TO START OVER USING A NEW KIT. PER THE CUSTOMER; THE PATIENT'S CONDITION DETERIORATED SHORTLY AFTER DISCONNECTION DUE TO UNDERLYING CONDITION THAT LEAD TO PATIENT EXPIRATION. DUE TO EU PERSONAL DATA PROTECTION LAWS; THE PATIENT INFORMATION IS NOT AVAILABLE FROM THE CUSTOMER. PATIENT GENDER AND WEIGHT WERE OBTAINED FROM THE RUN DATA FILE. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN BECAUSE IT WAS DISCARDED BY THE CUSTOMER. Manufacturer Narrative: INVESTIGATION: THE CUSTOMER STATED THAT THE HOSPITAL HAD PROBLEMS WHEN ATTEMPTING TO INSERT THE JUGULAR LINE INTO THE PATIENT. THE RUN DATA FILE (RDF) WAS ANALYZED FOR THIS EVENT. THE SPECTRA OPTIA MACHINE OPERATED AS INTENDED. THE SYSTEM WAS DETECTING CELLS IN THE PLASMA LINE FROM

THE CENTRIFUGE. IT IS POSSIBLE THAT THIS WAS RELATED TO THE DISEASE STATE OF THE PATIENT. THE ALARMS THAT OCCURRED WERE APPROPRIATE BASED ON WHAT WAS SEEN IN THE RBC DETECTOR. THE CELL'S WERE DETECTED IN PLASMA LINE FROM CENTRIFUGE. ALARMS OCCUR IF THE SYSTEM DETECTS THAT THE RG RATIO IS GREATER THAN 1.5. THIS INDICATES THAT THE SYSTEM IS SEEING SOMETHING UNUSUAL GOING THROUGH THE RBC DETECTOR. THIS ALARM MAY OCCUR FOR THE FOLLOWING REASONS: PATIENT RELATED DISEASE STATE. INACCURATE PATIENT HEMATOCRIT. HEMOLYSIS MAY HAVE OCCURRED PATIENT'S TTP MAY HAVE CONTRIBUTED TO THE ALARMS IN THIS PROCEDURE. THE MACHINE WAS CHECKED OUT AT THE CUSTOMER SITE BY A TERUMO BCT SERVICE TECHNICIAN. A FULL AUTOTEST AND SIMULATED USE SALINE RUN WERE PERFORMED WITH NO ISSUES FOUND. INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: INVESTIGATION: THE CUSTOMER DID NOT PROVIDE THE LOT NUMBER PERTAINING TO THIS EVENT; THEREFORE A DEVICE HISTORY RECORD (DHR) SEARCH COULD NOT BE CONDUCTED FOR THIS SPECIFIC INCIDENT. ALL LOTS MUST MEET ACCEPTANCE CRITERIA BEFORE RELEASE. ROOT CAUSE: PROVIDED BY THE CUSTOMER; CAUSE OF EXPIRY WAS DUE TO THE PATIENT CONDITION PRIOR TO BEING CONNECTED TO THE MACHINE. Manufacturer Narrative: INVESTIGATION: THE LOT NUMBER WAS CONFIRMED BY THE CUSTOMER; SO A REVIEW OF THE DEVICE HISTORY RECORD (DHR) FOR THIS UNIT WAS ABLE TO BE PERFORMED. THE DHR REVIEW SHOWED NO IRREGULARITIES DURING MANUFACTURING THAT WOULD HAVE CONTRIBUTED TO THE PATIENT'S EXPIRY AS EXPERIENCED BY THE CUSTOMER. ALL QUALITY LABS AND STERILIZATION REQUIREMENTS PASSED.

Death#2 (Report# 1722028-2015-00174)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT EXPIRED APPROXIMATELY 20 MINUTES INTO A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE. DURING THE PROCEDURE; THE PATIENT BECAME RESTLESS AND DEVELOPED TROUBLE BREATHING. A CODE WAS CALLED. THE PATIENT LATER EXPIRED AND THE PHYSICIAN WAS CALLED AT THE TIME OF DEATH. PER THE CUSTOMER; THE CAUSE OF DEATH WAS DUE TO THE PATIENT'S DISEASE CONDITION AND THEY DO NOT ALLEGE A DEFICIENCY WITH THE MACHINE OR THE DISPOSABLE SET. THE CUSTOMER DECLINED TO PROVIDE THE PATIENT IDENTIFIER. THE CUSTOMER DECLINED TO PROVIDE AN AUTOPSY OR DISCHARGE SUMMARY FOR THE PATIENT. Manufacturer Narrative: INVESTIGATION: PER THE CUSTOMER; FRESH FROZEN PLASMA (FFP) WAS BEING USED AS A REPLACEMENT. FLUIDS HANGING WERE ANTICOAGULANT AND NORMAL SALINE. THE RUN DATA FILE (RDF) WAS ANALYZED FOR

THIS EVENT. BASED ON THE RUN DATA FILE ANALYSIS; THE SPECTRA OPTIA SYSTEM OPERATED AS INTENDED. THE DISPOSABLE SET CONTAINING BLOOD AND AN AS TO TUBE LINE CONTAINING BLOOD WERE RETURNED FOR FURTHER INVESTIGATION. THE SET AND TUBING LINES WERE VISUALLY INSPECTED FOR KINKS; OCCLUSIONS; MISSING PARTS; MIS-ASSEMBLY AND LEAKS AND NONE WERE FOUND. THERE WERE NO SIGNS OF CLOTTING IN THE SET. THE MACHINE WAS CHECKED OUT AT THE CUSTOMER SITE BY A TERUMO BCT SERVICE TECHNICIAN. NONE OF THE CORRECTIONS LISTED IN THE SERVICE CALL FOR THE CRACKED DOOR HINGE OR THE COLUMN PRESSURE ARE RELATED TO THE PROCEDURE OR PATIENT DEATH. THE COLUMN PRESSURE IS NOT DONE ON TPE PROCEDURES. ROOT CAUSE: BASED ON THE PHYSICIAN'S STATEMENTS; THE CAUSE OF DEATH WAS DUE TO THE PATIENT DISEASE STATE.

Death#3 (Report# 1722028-2015-00126)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT UNDERGONE A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE AND SHE HAD A RESPIRATORY EVENT THAT LEAD TO HER EXPIRATION. APPROXIMATELY AN HOUR AFTER THE COMPLETION OF THE PROCEDURE; THE PATIENT SUFFERED A RESPIRATORY DISTRESS AND A MEDICAL CODE WAS CALLED. THE PATIENT LATER EXPIRED. THE CUSTOMER IS NOT ALLEGING A DEFICIENCY WITH THE DISPOSABLE SET OR DEVICE. THE CUSTOMER STATED THAT THE PATIENT WAS 'VERY' SICK AND THE PATIENT'S ILLNESS WAS THE CAUSE OF PATIENT EXPIRATION. THE CUSTOMER DECLINED TO PROVIDE PATIENT'S IDENTIFIER. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN BECAUSE IT WAS DISCARDED BY THE CUSTOMER. Manufacturer Narrative: INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: INVESTIGATION: THE CUSTOMER DECLINED TO PROVIDE THE PATIENT'S AUTOPSY OR DISCHARGE SUMMARY REPORT. ROOT CAUSE: THE RDF AND SERVICE CALL INDICATE THAT THE SYSTEM OPERATED AS INTENDED. THE PATIENT HAD A MEDICAL HISTORY INVOLVING CATASTROPHIC ANTIPHOSPHOLIPID ANTIBODY SYNDROME. BASED ON LITERATURE RESEARCH INDICATING THAT CATASTROPHIC APS HAS A HIGH MORTALITY RATE; THE CAUSE FOR THIS PATIENT DEATH IS RELATED TO THEIR COMPROMISED MEDICAL DISEASE STATE.

Death#4 (Report# 1722028-2015-00063)

Event Description: THE CUSTOMER REPORTED THAT THE PATIENT WAS UNDERGOING A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE AND SHE WENT INTO CARDIAC ARREST THAT LEAD TO

HER EXPIRATION. APPROXIMATELY 3 HOURS INTO THE PROCEDURE; HER HEART RATE DECREASED. THE PHYSICIAN WAS NOTIFIED AND A CODE WAS CALLED. THE CODE TEAM PERFORMED STANDARD PROCEDURE FOR CARDIAC ARREST; BUT WAS UNABLE TO REVIVE THE PATIENT. PER THE CUSTOMER; THE CAUSE OF DEATH WAS RELATED TO THE PATIENT'S DISEASE PROGRESSION AND THEY DID NOT ALLEGE A DEFICIENCY WITH THE SYSTEM OR DISPOSABLE. THE CUSTOMER DECLINED TO PROVIDE PATIENT IDENTIFIER; AGE AND WEIGHT. PATIENT WEIGHT AND GENDER WERE OBTAINED FROM THE RUN DATA FILE. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN BECAUSE IT WAS DISCARDED BY THE CUSTOMER.

Manufacturer Narrative: (B)(4) MANUFACTURING REVIEW AND STERILIZATION PROCESS REVIEW INVESTIGATION: FLUIDS USED DURING THE PROCEDURE WERE ANTICOAGULANT (ACDA); SALINE (B)(4) AND FRESH FROZEN PLASMA (FFP) WAS USED FOR REPLACEMENT FLUID. THE CUSTOMER STATED THAT THE PATIENT HAD TTP; SUFFERED LABORED BREATHING; AND HAD LOW OXYGEN SATURATION LEVELS BEFORE THE PROCEDURE BEGAN.

FUNCTIONAL CHECKOUT OF THE MACHINE WAS PERFORMED BY A TERUMO BCT SERVICE TECHNICIAN. ALL FUNCTIONAL TESTS MET SPECIFICATIONS. A SALINE RUN WITH ALL ALARM TESTS WAS PERFORMED WITHOUT FAILURE. ALL TESTS PASSED. THE RUN DATA FILE (RDF) WAS ANALYZED FOR THIS EVENT. THE SIGNALS IN THE RDF INDICATED THAT THE SYSTEM OPERATED AS INTENDED.

ACCORDING TO A PUBLISHED ARTICLE IN THE AMERICAN JOURNAL OF EMERGENCY MEDICINE; CARDIAC ARREST CAN BE LINKED TO TTP DISORDER. BECAUSE TTP IS A DISEASE CHARACTERIZED BY THROMBI IN MICRO CIRCULATION THROUGHOUT THE BODY; THE FLOW OF BLOOD TO THE LUNGS CAN BECOME LIMITED OR BLOCKED. WHEN THIS OCCURS; IT IS REFERRED TO AS PULMONARY EMBOLISM. FULMINANT PE SHOWS A HIGH PREVALENCE AND OFTEN DEGENERATES INTO CARDIOPULMONARY ARREST. SPECTRA OPTIA APHERESIS ESSENTIALS GUIDE PROVIDES THE FOLLOWING CAUTIONS: "THE PHYSIOLOGICAL CONDITION OF PATIENTS MAY AFFECT THE OUTCOMES OF PROCEDURES PERFORMED ON THE SPECTRA OPTIA SYSTEM." A REVIEW OF THE DEVICE HISTORY RECORD (DHR) FOR THIS UNIT SHOWED NO IRREGULARITIES DURING MANUFACTURING THAT WERE RELEVANT TO THIS ISSUE.

THE PATIENT'S OFFICIAL RELEASE RECORD AND/OR AUTOPSY REPORT WERE REQUESTED FROM THE HOSPITAL'S MEDICAL RECORDS DEPARTMENT. INFORMATION; SUCH AS NAME; DOB; AND SSN; WAS STATED AS NECESSARY TO OBTAIN THOSE RECORDS.

PREVIOUS ATTEMPTS TO OBTAIN THE PATIENT ID WERE UNSUCCESSFUL AND THEREFORE; THE OFFICIAL MEDICAL REPORT(S) COULD NOT BE OBTAINED. ROOT CAUSE: THE DEFINITIVE CAUSE FOR THE PATIENT'S DEATH IS UNDETERMINED BUT IS NOT

ALLEGED TO BE DUE TO THE SPECTRA OPTIA SYSTEM. BASED ON THE NURSE'S DESCRIPTION OF EVENTS; DLOG ANALYSIS; AND MACHINE SERVICE INSPECTION; THE LIKELY ROOT CAUSE WAS THE PATIENT'S DISEASE STATE; BUT THIS COULD NOT BE CONFIRMED BY THE PHYSICIAN OR WITH MEDICAL RECORDS.

Death#5 (Report# 1722028-2014-00411)

Event Description: THE CUSTOMER REPORTED THAT A PRIMATE EXPIRED 2 DAYS AFTER A MONONUCLEAR CELL (MNC) COLLECTION PROCEDURE. THE CUSTOMER STATED THAT DURING THE PROCEDURE ON (B)(6) 2014; THEY HAD SOME ACCESS ISSUES AND SOME CLUMPING IN THE INLET MANIFOLD; THEN A LEAK DETECTED ALARM THAT THEY COULDN'T CLEAR. THEY KEPT THE ANIMAL ANESTHETIZED BY GAS AND HE RECOVERED AFTER THE PROCEDURE; BUT WAS 'OFF'. HE WENT INTO ACUTE RENAL FAILURE AND DISSEMINATED INTRAVASCULAR COAGULATION (DIC) AND EXPIRED ON (B)(6) 2014. THE CUSTOMER IS NOT ALLEGING A DEFICIENCY WITH THE DISPOSABLE SET OR DEVICE. THE DISPOSABLE KIT IS NOT AVAILABLE FOR RETURN BECAUSE IT WAS DISCARDED BY THE CUSTOMER. THIS REPORT IS BEING FILED DUE TO A PATIENT ((B)(6)) DEATH; THOUGH AT THIS TIME; THE DEVICE IS NOT SUSPECTED OR ALLEGED TO BE A CONTRIBUTORY FACTOR IN THE DEATH. Manufacturer Narrative: INVESTIGATION: AN INTERNAL INVESTIGATION HAS BEEN INITIATED AT THE CUSTOMER'S SITE. THE CUSTOMER STATED THAT THEY ARE INVESTIGATING IF THE (B)(6) HAD ANY PRE-DISPOSING ISSUES THAT WOULD HAVE CAUSED THE DEATH. THE CUSTOMER REQUESTED FOR RE-TRAINING ON THE SPECTRA OPTIA MACHINE. TERUMO BCT SERVICE REPRESENTATIVE PERFORMED A FULL FUNCTIONAL CHECK; INCLUDING THE LEAK DETECTOR; ON THE SPECTRA OPTIA DEVICE WITH NO DISCREPANCIES FOUND. THE PROBLEM COULD NOT BE DUPLICATED DURING CHECKOUT. THE RUN DATA FILE (RDF) WAS ANALYZED FOR THIS EVENT. THERE WERE SEVERAL ALARMS DURING THIS PROCEDURE WHICH ARE NOT UNCOMMON TO OCCUR DURING PROCEDURES ON SMALL PATIENTS WITH A SMALL TOTAL BLOOD VOLUME. AS THE PROCEDURE PROGRESSED THE SYSTEM PREDICTED THAT THE FLUID BALANCE LIMITS WOULD BE EXCEEDED BASED ON THE CURRENTLY ENTERED PATIENT INFORMATION AND RUN VALUES; AND REQUIRED OPERATOR CONFIRMATION IN ORDER TO CONTINUE WITH THE COLLECTION. THE SIGNALS IN THE RUN DATA FILE INDICATE THAT THE SPECTRA OPTIA SYSTEM OPERATED AS INTENDED AND IS SAFE TO USE. INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Death#6 (Report# 1722028-2014-00391)

Event Description: THE CUSTOMER REPORTED THAT A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE WAS BEING PERFORMED ON A PATIENT IN ICU. PER THE CUSTOMER; THE PATIENT ALREADY HAD LABORED BREATHING AND OXYGEN SATURATIONS WERE AROUND 86 PRIOR TO THE START OF PROCEDURE. APPROXIMATELY 2 MINUTES INTO THE PROCEDURE; THE PATIENT STOPPED BREATHING AND A CODE WAS CALLED. THE CODE TEAM WAS UNABLE TO REVIVE THE PATIENT. THE CUSTOMER DECLINED TO PROVIDE PATIENT'S IDENTIFIER. THE DISPOSABLE KIT IS NOT AVAILABLE FOR RETURN BECAUSE IT WAS DISCARDED BY THE CUSTOMER. THIS REPORT IS BEING FILED DUE TO PATIENT DEATH; ALTHOUGH THERE IS NO ALLEGED DEVICE INVOLVEMENT OR MALFUNCTION.

Manufacturer Narrative: INVESTIGATION: PER THE CUSTOMER; THE MINIMUM WEIGHT SHE COULD ENTER IN THE SPECTRA OPTIA SYSTEM WAS (B)(6) LBS DUE TO THE OPTIA RANGE. INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

2013-2014

Death#1 (Report# 1722028-2013-01531)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT WITH A LOW HEMATOCRIT OF 15% WAS UNDERGOING A THERAPEUTIC PLASMA EXCHANGE (TPE). THE PATIENT RECEIVED SEVERAL UNITS OF BLOOD BEFORE THE PROCEDURE AND BLOOD PRIME WAS NOT PERFORMED. THE CUSTOMER STATED THAT 30 MINUTES INTO THE PROCEDURE, PLASMA WAS NOT YET BEING EXCHANGED. THE OPERATOR COULD NOT SEE AN INTERFACE IN THE CHANNEL, AND SHE WAS NOT ABLE TO CHANGE THE INLET FLOW RATE. THE CUSTOMER DECIDED TO PERFORM RINSE BACK, AND THE PATIENT WAS TAKEN OFF OF THE MACHINE. THE PATIENT LATER EXPIRED. PATIENT IDENTIFIER, AGE AND WEIGHT ARE NOT AVAILABLE AT THIS TIME. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN FOR ANALYSIS BECAUSE THE CUSTOMER DISCARDED IT. THIS REPORT IS BEING FILED DUE TO A PATIENT DEATH, THOUGH AT THIS TIME IT IS NOT ALLEGED OR SUSPECTED THAT THE DEVICE CONTRIBUTED TO THE DEATH. Event Description: PER THE CUSTOMER, THE PATIENT'S WEIGHT WAS NOT AVAILABLE. Manufacturer Narrative: INVESTIGATION: THE DISPOSABLE SET WAS UNAVAILABLE FOR RETURN AND ANALYSIS. A SERVICE CALL WAS PLACED ON THE DEVICE. ALL FUNCTIONS PASSED SUCCESSFULLY DURING THE DEVICE AUTOTEST AND A SALINE RUN WAS PERFORMED AND VERIFIED THE PROPER OPERATION OF THE SPECTRA OPTIA. LATER IN THE DAY AFTER THE TPE PROCEDURE WAS ENDED AND THE PATIENT WAS OFF THE MACHINE, THE PATIENT EXPERIENCED AN

OXYGEN SATURATION OF 93 ON A 6L NASAL CANNULA. THE PATIENT WAS DESATURATED TO THE 80S AND PLACED ON A NON-REBREATHER. THE PATIENT THEN BECAME UNRESPONSIVE, AND PROGRESSED TO ASYSTOLE. CPR WAS INITIATED AND THE PATIENT WAS INTUBATED. THE PATIENT REPEATEDLY WENT INTO CARDIAC ARREST DESPITE THE CPR. THE FAMILY THEN MADE THE PATIENT A DNR. THE CUSTOMER STATED THAT THIS PATIENT DIED DUE TO THEIR DISEASE STATE AND THAT THE TPE PROCEDURE WAS NOT INVOLVED IN THIS DEATH. ROOT CAUSE: BASED ON THE EVALUATION OF THE DEVICE AND THE CUSTOMER'S EVALUATION OF THE PATIENT, THE CAUSE OF DEATH WAS DUE TO THE PATIENT'S DISEASE STATE. THE CAUSE OF THE INITIAL PERFORMANCE ISSUE WAS THE LOW HEMATOCRIT OF THE PATIENT, WHICH PREVENTED THE DEVICE FROM ESTABLISHING AN INTERFACE IN THE CHANNEL. THE DEVICE IS DESIGNED TO REQUIRE A MINIMUM HEMATOCRIT FOR THE PROCEDURE AND THEREFORE INHERENTLY PREVENTS PROCEDURES WITH LOW HEMATOCRITS FROM BEING ABLE TO BE PERFORMED. Manufacturer Narrative: INVESTIGATION: THE MACHINE REQUIRES A CERTAIN HEMATOCRIT TO SET UP THE INTERFACE, AND THE PATIENT'S HEMATOCRIT WAS TOO LOW TO ACCOMPLISH THIS. IT WAS SUGGESTED TO THE CUSTOMER AT THE TIME OF THE INITIAL CALL TO CONTACT THE PHYSICIAN ABOUT GIVING THE PATIENT MORE BLOOD OR DOING A BLOOD PRIME, WHICH WOULD ALLOW THEM TO SET UP THE INTERFACE WITHOUT TAKING OUT AS MUCH OF THE PATIENT'S BLOOD. INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED

Death#2 (Report# 1722028-2014-00252)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT IN ICU WAS UNDERGOING A THERAPEUTIC PLASMA EXCHANGE(TPE) PROCEDURE IN TANDEM WITH CONTINUOUS VENO-VENOUS HEMOFILTRATION (CVVH). APPROXIMATELY 15 MINUTES PRIOR TO COMPLETION OF THE TPE PROCEDURE, THE PATIENT WAS COUGHING, COMPLAINED THAT HIS THROAT WAS HURTING AND FELT SHORT OF BREATH. THE PATIENT'S HEART RATE AND O₂ SATURATION DECREASED. THE ICU NURSE CALLED A CODE AND ATTEMPTED INTUBATION. THE PATIENT THEN EXPIRED AFTER THE CODE WAS CALLED. THE DISPOSABLE SET WAS NOT AVAILABLE FOR RETURN FOR EVALUATION BECAUSE IT WAS DISCARDED BY THE CUSTOMER. THIS REPORT IS BEING FILED DUE TO PATIENT DEATH, THOUGH AT THIS TIME IT IS NOT SUSPECTED OR ALLEGED THAT THE DEVICE WAS A CONTRIBUTORY FACTOR. Manufacturer Narrative: INVESTIGATION: THE RUN DATA FILE (RDF) WAS ANALYZED. THE SIGNALS IN THE RUN DATA FILE INDICATE THAT

THE SPECTRA OPTIA SYSTEM OPERATED AS INTENDED. INVESTIGATION IS IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: INVESTIGATION: A REVIEW OF THE DEVICE HISTORY RECORD (DHR) FOR THIS UNIT SHOWED NO IRREGULARITIES DURING MANUFACTURING THAT WERE RELEVANT TO THIS ISSUE. A SERVICE CALL WAS PLACED AND A FULL MACHINE CHECKOUT WAS PERFORMED. THE MACHINE IS FUNCTIONING PER MANUFACTURERS SPECIFICATION. A REVIEW OF THE LOT FOR SIMILAR REPORTS WAS CARRIED OUT AND NONE HAVE BEEN REPORTED. MULTIPLE ATTEMPTS TO GATHER FURTHER INFORMATION REGARDING THE PROCEDURE AND AUTOPSY RESULTS REMAIN UNANSWERED. ROOT CAUSE: THIS DISPOSABLE SET WAS UNAVAILABLE FOR SPECIFIC ROOT CAUSE ANALYSIS. THE RDF AND THE SERVICE CALL SHOW THAT THE SYSTEM OPERATED AS INTENDED. A DEFINITIVE ROOT CAUSE COULD NOT BE DETERMINED. BASED ON THE STATEMENTS FROM THE CUSTOMER, POSSIBLE CAUSES INCLUDE BUT ARE NOT LIMITED TO COMPROMISED PATIENT PHYSIOLOGY OR RELATED TO HOW THE CVVH PROCEDURE INTERACTED WITH THE APHERESIS PROCEDURE. SPECTRA OPTIA APHERESIS SYSTEM ESSENTIALS GUIDE OFFERS THE FOLLOWING PROCEDURAL CAUTION: "THE SPECTRA OPTIA SYSTEM HAS MANY SAFETY FEATURES. HOWEVER, A PATIENT REACTION CAN OCCUR RAPIDLY. THEREFORE, IT IS IMPERATIVE THAT THE OPERATOR MONITOR THE PATIENT AND THE SYSTEM THROUGHOUT THE PROCEDURE." Manufacturer Narrative: INVESTIGATION: PER THE CUSTOMER, THE PATIENT HAD BEEN TREATED IN (B)(6) AT A SISTER FACILITY WHERE HE WAS ADMITTED AND HAD 5 TPE PROCEDURES IN TANDEM WITH CVVH. HE HAD BEEN INTUBATED AT THAT TIME. HE WAS SEPTIC WITH LOSS OF CONSCIOUSNESS CHANGES, MULTIPLE SYSTEM ORGAN FAILURE, RESPIRATORY PROBLEMS AND STROKE. HE WAS SENT TO THE CURRENT FACILITY FOR REHAB. HE WAS ON O2 BY CANNULA, BREATHING ON HIS OWN, ALERT, AND TALKING WITH HIS BROTHER DURING THE PROCEDURE. INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: ADDITIONAL INFORMATION: THE MEDICAL DIRECTOR STATED THAT THE PATIENT DEATH WAS DUE TO PULMONARY EMBOLUS.

Death#3 (Report# 1722028-2014-00252 and Report# 1722028-2014-00229)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT UNDERWENT A RED BLOOD CELL EXCHANGE (RBCX) PROCEDURE. THE PATIENT WAS DISCHARGED AFTER THE COMPLETION OF THE PROCEDURE ON (B)(6) 2014. APPROXIMATELY 24 HOURS AFTER THE DISCHARGE, THE PATIENT SUFFERED A STROKE AND HEAD BLEED. THE PATIENT WAS TAKEN TO THE EMERGENCY ROOM AND

ADMITTED TO THE HOSPITAL. THE PATIENT EXPIRED ON (B)(6) 2014. THE DISPOSABLE KIT IS NOT AVAILABLE FOR RETURN BECAUSE IT WAS DISCARDED BY THE CUSTOMER. THIS REPORT IS BEING FILED DUE TO PATIENT DEATH, THOUGH AT THIS TIME IT IS NOT BELIEVED THAT THE DEVICE CAUSED OR CONTRIBUTED TO THE PATIENT DEATH. Manufacturer Narrative: INVESTIGATION: PER THE CUSTOMER, THE MEDICAL DIRECTOR AT THIS PROGRAM WAS CONSULTED AND STATED THE DEATH HAD NOTHING TO DO WITH THE DEVICE. HE STATED THAT THE PATIENT WAS VERY OLD FOR A SICKLE CELL PATIENT AND THEY ARE LEARNING WHAT OTHER COMPLICATIONS PRESENT AT THAT AGE FOR A SICKLE CELL PATIENT. INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: INVESTIGATION: THE DISPOSABLE SET WAS UNAVAILABLE FOR RETURN AND INVESTIGATION. A REVIEW OF THE DEVICE HISTORY RECORD (DHR) FOR THIS UNIT SHOWED NO IRREGULARITIES DURING MANUFACTURING THAT WERE RELEVANT TO THIS ISSUE. A REVIEW OF THE LOT FOR SIMILAR REPORTS WAS CARRIED OUT AND NONE HAVE BEEN REPORTED. MULTIPLE ATTEMPTS TO OBTAIN THE DISCHARGE SUMMARY AND AUTOPSY REPORT OF THE PATIENT WERE UNANSWERED BY THE CUSTOMER. ROOT CAUSE: THE ROOT CAUSE REMAINS UNDETERMINED AT THIS TIME DUE TO LIMITED INFORMATION OBTAINED. NO FAILURE OF THE DEVICE WAS DETECTED IN THE RDFS OR DHR. PER THE MEDICAL DIRECTOR, THE DEATH WAS UNRELATED TO THE RBCX PROCEDURE. Manufacturer Narrative: INVESTIGATION: THE RUN DATA FILE (RDF) WAS ANALYZED FOR THIS EVENT. THE SIGNALS IN THE RUN DATA FILE INDICATE THAT THE SPECTRA OPTIA SYSTEM IS SAFE TO USE AND OPERATED AS INTENDED. INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Death#4 (Report# 1722028-2014-00230)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT UNDERWENT A RED BLOOD CELL EXCHANGE (RBCX) PROCEDURE. DURING THE PROCEDURE, THE PATIENT DEVELOPED ITCHING ON THE FACE AND NECK. DIPHENHYDRAMINE AND ACETAMINOPHEN WERE GIVEN IN RESPONSE TO THE PATIENT REACTION. AT THE COMPLETION OF THE RBCX, THE PATIENT WAS DISCHARGED HOME. PER THE CUSTOMER, APPROXIMATELY ONE WEEK LATER, THE PATIENT WAS FOUND UNCONSCIOUS AT HOME AND WAS ADMITTED THROUGH THE ER TO NEUROSURGERY SERVICE. AN MRI WAS GIVEN AND THE PATIENT WAS HOSPITALIZED IN THE ICU. PATIENT DEVELOPED A HEMORRHAGE SECONDARY TO MOYAMOYA AND EXPIRED ON (B)(6) 2014. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN FOR EVALUATION BECAUSE THE CUSTOMER

DISCARDED IT. THIS REPORT IS BEING FILED DUE TO PATIENT DEATH, THOUGH AT THIS TIME, THE DEVICE IS NOT SUSPECTED OR ALLEGED TO BE A CONTRIBUTORY FACTOR IN THE DEATH.

Manufacturer Narrative: INVESTIGATION: PER THE CUSTOMER, THE MEDICAL DIRECTOR AT THIS PROGRAM WAS CONSULTED HE STATED THE DEATH HAD NOTHING TO DO WITH THE DEVICE. HE STATED THAT THE PATIENT WAS VERY OLD FOR A SICKLE CELL PATIENT AND THEY ARE LEARNING WHAT OTHER COMPLICATIONS PRESENT AT THAT AGE FOR A SICKLE CELL PATIENT.

INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: INVESTIGATION: THE RUN DATA FILE (RDF) WAS ANALYZED FOR THIS EVENT. SIGNALS IN THE RDF INDICATE THAT THE SPECTRA OPTIA SYSTEM IS SAFE AND OPERATED AS INTENDED. INVESTIGATION IS IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Manufacturer Narrative: INVESTIGATION: THE DISPOSABLE SET WAS UNAVAILABLE FOR RETURN AND INVESTIGATION. A REVIEW OF THE DEVICE HISTORY RECORD (DHR) FOR THIS UNIT SHOWED NO IRREGULARITIES DURING MANUFACTURING THAT WERE RELEVANT TO THIS ISSUE. A REVIEW OF THE LOT FOR SIMILAR REPORTS WAS CARRIED OUT AND NONE HAVE BEEN REPORTED. ROOT CAUSE: NO FURTHER INFORMATION WAS PROVIDED BY THE CUSTOMER. BASED ON THE INFORMATION THAT WAS PROVIDED BY THE CUSTOMER, THE ROOT CAUSE OF PATIENT'S CONDITION WAS HEMORRHAGE SECONDARY TO MOYAMOYA. NO FAILURE WAS DETECTED WITH THE DEVICE.

Death#5 (Report# 1722028-2014-00145)

Event Description: THE CUSTOMER REPORTED THAT A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE WAS BEING PERFORMED ON A PATIENT IN ICU. APPROXIMATELY 30 MINUTES INTO THE PROCEDURE, THE PATIENT'S HEART RATE DROPPED AND A CODE WAS CALLED BY THE ICU STAFF. ACLS AND CPR WERE GIVEN TO THE PATIENT. RINSEBACK WAS PERFORMED DURING THE CODE. THEY WERE ABLE TO GET A HEART RATE AND PROCEEDED TO RESTART THE PROCEDURE, BUT THE PATIENT'S HEART RATE DROPPED AGAIN SOON AFTER. THE PATIENT EXPIRED ON (B)(6) 2014. THE CUSTOMER DECLINED TO PROVIDE PATIENT'S IDENTIFIER. THE DISPOSABLE KIT IS NOT AVAILABLE FOR RETURN BECAUSE IT WAS DISCARDED BY THE CUSTOMER. THIS REPORT IS BEING FILED DUE TO PATIENT DEATH, ALTHOUGH THERE IS NO ALLEGED DEVICE INVOLVEMENT OR MALFUNCTION.

Manufacturer Narrative: INVESTIGATION: A REVIEW OF THE DEVICE HISTORY RECORD (DHR) FOR THIS UNIT SHOWED NO IRREGULARITIES DURING MANUFACTURING THAT WERE RELEVANT TO THIS ISSUE.

ATTEMPTS MADE TO GATHER THE PATIENT'S DISCHARGE SUMMARY

WERE UNSUCCESSFUL. THE RUN DATA FILE (RDF) WAS ANALYZED FOR THIS EVENT. THE RUN DATA FILE ANALYSIS SHOWS THAT THE MULTIPLE "CELLS DETECTED IN THE PLASMA LINE ALARMS" WERE LIKELY CAUSED BY HEMOLYSIS. THE HEMOLYSIS IS LIKELY DUE TO THE PATIENT'S CONDITION OF THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP). A SERVICE CALL WAS PLACED TO HAVE THE OPTIA EQUIPMENT INVOLVED IN THE EVENT CHECKED OUT AT THE CUSTOMER SITE. A FULL CHECKOUT AND A SALINE SIMULATED RUN WERE PERFORMED. NO ISSUES OR ABNORMAL CONDITIONS WERE NOTED. ROOT CAUSE: BASED ON THE PATIENT INFORMATION, THE CUSTOMER'S DESCRIPTION OF THE PROCEDURE, AND THE RUN DATA FILE ANALYSIS, THE CAUSE OF DEATH WAS THE PATIENT'S DISEASE STATE. Manufacturer Narrative: INVESTIGATION: PER THE CUSTOMER, THE ATTENDING MEDICAL DIRECTOR HAD ORDERED PLATELETS PRIOR TO THE EVENT TO BE GIVEN TO PATIENT. THE PATIENT DEVELOPED A REACTION TO THE PLATELETS, SO A TPE WAS ORDERED. THE PHYSICIAN DIDN'T WANT TO GIVE ANY BLOOD PRIOR TO THE TPE DUE TO THE PATIENT'S REACTION TO THE PLATELETS. THE OPERATOR ORIGINALLY CONTACTED TERUMO BCT'S CLINICAL SUPPORT LINE DUE TO "CELLS DETECTED IN PLASMA LINE" ALARM. THE OPERATOR STATED THAT SHE COULDN'T SEE AN INTERFACE, AND THAT SHE DIDN'T SEE ANY PLASMA IN THE REMOVE BAG. SHE ALSO STATED THAT THE REPLACEMENT FLUID WASN'T DRIPPING. INVESTIGATION IS IN PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

2012-2013

Death#1 (Report# 1722028-2013-01278)

Event Description: THE CUSTOMER REPORTED THAT THE PATIENT WAS UNDERGOING A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE AND SHE HAD A CARDIAC EVENT THAT LEAD TO HER EXPIRATION AFTER THE RINSEBACK WAS COMPLETED. THE PATIENT HAD A SEIZURE-LIKE ACTIVITY. SHE HAD A NORMAL HEART RHYTHM; O2 STATS WERE 100%; THEN HER BLOOD PRESSURE DROPPED AND HER HEART RATE ELEVATED. ATRIAL FIBRILLATION OCCURRED AND THE PHYSICIAN DECIDED TO DO CARDIOVERSION. SHE WENT INTO ASYSTOLE AFTER THE CARDIOVERSION AND THEY CALLED A CODE. CPR WAS GIVEN IN ATTEMPT TO RESUSCITATE THE PATIENT; BUT THE PATIENT EXPIRED. PER THE CUSTOMER; THE PATIENT'S INCIDENT IS NOT RELATED TO THE APHERESIS MACHINE OR THE DISPOSABLE APHERESIS SET USED DURING THE PROCEDURE. THE DISPOSABLE SET IS UNAVAILABLE FOR RETURN BECAUSE THE CUSTOMER DISCARDED IT. THIS REPORT IS BEING FILED DUE TO PATIENT DEATH; ALTHOUGH PER CURRENT

INFORMATION THERE IS NO MALFUNCTION WITH THE TERUMO BCT DEVICE OR ALLEGATION OF A MALFUNCTION. Manufacturer Narrative: INVESTIGATION: PER THE CUSTOMER; THE MACHINE FUNCTIONED NORMALLY WITH NO ALARMS. THE MACHINE WAS CHECKED OUT BY A TERUMO BCT SERVICE TECHNICIAN. THERE WERE NO ISSUES FOUND DURING CHECKOUT THAT WERE RELATED TO THIS EVENT AND THE MACHINE WAS RELEASED FOR USE. INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Death#2 (Report# 1722028-2013-01265)

Event Description: THE CUSTOMER REPORTED THAT A PATIENT UNDERWENT A THERAPEUTIC PLASMA EXCHANGE (TPE)PROCEDURE. THE PATIENT COMPLETED THE PROCEDURE WITH NO REACTIONS. HE WAS SENT TO INTERVENTIONAL RADIOLOGY TO HAVE HIS CENTRAL VENOUS CATHETER REMOVED. FOLLOWING REMOVAL OF THE CATHETER; HE DEVELOPED SHORTNESS OF BREATH AND WAS SENT TO THE EMERGENCY ROOM. THE PATIENT WAS ADMITTED TO THE INTENSIVE CARE UNIT AND THE SHORTNESS OF BREATH LEAD TO RESPIRATORY FAILURE AND THE PATIENT EXPIRED THAT DAY. THE CUSTOMER CONTACTED TERUMO BCT TO INQUIRE ABOUT COMPLAINTS RELATED TO THE LOT NUMBERS USED DURING THE PROCEDURE. THE PATIENT IDENTIFIER IS NOT AVAILABLE PER THE CUSTOMER. THIS REPORT IS BEING FILED DUE TO A PATIENT DEATH; THOUGH AT THIS TIME; THE SPECTRA OPTIA SYSTEM HAS NOT BEEN IMPLICATED IN THE PATIENT DEATH. Manufacturer Narrative: INVESTIGATION: THE DISPOSABLE SET; WITH 4L OF PATIENT PLASMA PACKED ON WET ICE; WAS RETURNED FOR EVALUATION. THE PLASMA WAS STRAW-COLORED WITHOUT ANY RED TINGE. HEMOLYSIS TESTING WAS PERFORMED ON THE PATIENT PLASMA AND BLOOD FROM THE CHANNEL; WITH NO HEMOLYSIS FOUND. THE SET WAS INSPECTED FOR MISASSEMBLY; MISSING PARTS; KINKS; AND OCCLUSIONS; NONE WERE FOUND. THE RUN DATA FILE WAS ANALYZED FOR THIS EVENT. THE SIGNALS IN THE RUN DATA FILE AS WELL AS THE AIM SYSTEM IMAGES INDICATE THAT THE SPECTRA OPTIA SYSTEM OPERATED AS INTENDED. THE CUSTOMER WAS PROVIDED COMPLAINT INFORMATION RELATED TO THE LOT NUMBERS USED DURING THE PROCEDURE - THERE WERE NO OTHER REPORTABLE EVENTS ASSOCIATED WITH THESE LOT NUMBERS. INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Death#3 (Report# 1722028-2013-01151)

Event Description: THE CUSTOMER DECLINED TO PROVIDE THE PATIENT'S IDENTIFIER OR AGE. Manufacturer Narrative: THIS REPORT IS BEING FILED TO PROVIDE ADDITIONAL INFORMATION. INVESTIGATION: A REVIEW OF THE DEVICE HISTORY RECORD (DHR) FOR THIS UNIT SHOWED NO IRREGULARITIES DURING MANUFACTURING THAT WERE RELEVANT TO THIS ISSUE. THE RUN DATA FILE (RDF) WAS ANALYZED FOR THIS EVENT. SIGNALS IN THE RDF SHOWED THE RBC DETECTOR BEGAN TO CHANGE INDICATING AN INCREASE IN THE CONCENTRATION OF CELLS IN THE PLASMA LINE. IF THIS HAD CONTINUED THE 'CELLS WERE DETECTED IN THE PLASMA LINE FROM THE CENTRIFUGE' ALARM WOULD HAVE BEEN TRIGGERED. POSSIBLE CAUSES OF THIS ALARM INCLUDE AN AIR BUBBLE IN FRONT OF THE RBC DETECTOR; AN INCORRECTLY ENTERED PATIENT HEMATOCRIT OR THE OCCURRENCE OF HEMOLYSIS. THERE WERE NO OTHER EQUIPMENT ALARMS OR OTHER INDICATIONS OF A MALFUNCTIONING MACHINE. THE SYSTEM OPERATED AS INTENDED THOUGH AN OPERATOR INTERACTION CANNOT BE RULED OUT. ROOT CAUSE: BASED ON THE PHYSICIAN'S EVALUATION OF THE PATIENT; THE REVIEW OF THE RDF FOR THE PROCEDURE; AND THE EVALUATION OF THE MACHINE; THE ROOT CAUSE FOR THE DEATH IS THE PATIENT'S DISEASE STATE. Event Description: THE CUSTOMER REPORTED THAT A PATIENT EXPIRED DURING A THERAPEUTIC PLASMA EXCHANGE PROCEDURE. A 85% FLUID BALANCE WAS USED DURING THE PROCEDURE. THE CUSTOMER IS NOT WILLING TO SHARE FURTHER DETAILS OF THE EVENT. PER THE CUSTOMER; THE PATIENT WAS IN CRITICAL CONDITION ALREADY AND DIED OF CARDIAC ARREST; AUTONOMIC DYSFUNCTION. THE CUSTOMER (PHYSICIAN) STATED THAT THE DEATH WAS NOT RELATED TO THE OPTIA. PATIENT INFORMATION IS NOT AVAILABLE AT THIS TIME. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN BECAUSE THE CUSTOMER DISCARDED IT. THIS REPORT IS BEING FILED DUE TO A PATIENT DEATH; HOWEVER; THE PATIENT DEATH IS ATTRIBUTED TO THE PATIENT'S DISEASE STATE. Manufacturer Narrative: INVESTIGATION: THE DAY FOLLOWING THE REPORTED INCIDENT ((B)(6) 2013); TERUMO ENGINEERS CHECKED THE OPTIA MACHINE. AN AUTOTEST WAS RUN ON THE EQUIPMENT. ALL TESTS PASSED AND NO ISSUES WERE FOUND. THE SYSTEM WAS THOROUGHLY CHECKED AND PROPER FUNCTION WAS CONFIRMED ON (B)(4) 2013. OPTIA TPE PROCEDURE REVISION TRAINING WAS PROVIDED TO THE OPERATORS AT THE CUSTOMER SITE. DURING THE TRAINING; TERUMO BCT PARTICULARLY REINFORCED THE ANTICOAGULANT (AC); FLUID BALANCE (FB) MANAGEMENT BASED ON TOTAL BLOOD VOLUME (TBV) ON THE SYSTEM; AND THE CHOICE OF REPLACEMENT FLUID AS WELL AS SOME PRACTICE STATED IN THE 'APHERESIS PRINCIPLES AND PRACTICE' ABOUT FLUID BALANCE

REPLACEMENT FLUID; THE POTENTIAL CONSEQUENCE OF HYPOVOLEMIC EXCHANGE (I.E. HYPOTENSION).TERUMO BCT DEMONSTRATED THE IMPACT THAT DIFFERENT REPLACEMENT FLUIDS HAD ON THE PROCEDURE PARAMETERS. THE NURSES ALSO SHARED THE REASON FOR 85% FB USED: IT WAS TO PREVENT FLUID OVERLOAD DURING THE PROCEDURE BECAUSE SALINE WAS USUALLY INFUSED TO THE PATIENTS PRIOR TO THE PROCEDURE .INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Death#4 (Report# 1722028-2013-00981)

Event Description: THE CUSTOMER DECLINED TO PROVIDE THE PATIENT'S IDENTIFIER. Manufacturer Narrative: INVESTIGATION: A SERVICE CALL WAS PLACED FOR THE MACHINE. SIMULATED TREATMENT AND AN AUTOTEST WERE PERFORMED WITHOUT ANY PROBLEMS. AFTER THE SERVICE CALL FOUND NO PROBLEMS WITH THE SYSTEM; THE EQUIPMENT WAS PLACED BACK IN SERVICE. THERE HAVE BEEN NO OTHER REPORTS OF PROBLEMS WITH THIS SYSTEM SINCE THE REPORTED INCIDENT. PER THE CUSTOMER; THE PATIENT DEATH WAS DUE TO HIS DISEASE STATE (AML; SEPTIC; AND GRAPH VS. HOST DISEASE). PER THE CUSTOMER; NEITHER THE SPECTRA OPTIA DISPOSABLE SET NOR THE SPECTRA OPTIA SYSTEM IS SUSPECTED OF BEING RELATED TO THE PATIENT'S DEATH. INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED Manufacturer Narrative: THIS REPORT IS BEING FILED TO PROVIDE ADDITIONAL INFORMATION. INVESTIGATION: THE DEVICE HISTORY RECORDS (DHR) WERE REVIEWED FOR THIS LOT. THERE WERE NO EVENTS NOTED IN THE DHR THAT WOULD HAVE CONTRIBUTED TO THE ALARMS EXPERIENCED BY THE CUSTOMER. THE CUSTOMER CONFIRMED THAT NO TPE OR HEMODIALYSIS PROCEDURES WERE BEING PERFORMED AT THE TIME OF THE PATIENT'S DEATH. THE SPECTRA OPTIA FUNCTIONED AS INTENDED IN BOTH PROCEDURES. THERE IS NO SAFETY ISSUE ASSOCIATED WITH THE REPORTED CONDITION AS THE MACHINE ALARMED AS DESIGNED; PLACING THE DEVICE INTO A SAFE STATE. A REVIEW OF THE LOT FOR SIMILAR REPORTS WAS CARRIED OUT; NONE HAVE BEEN REPORTED. THE CUSTOMER DECLINED REQUESTS TO PROVIDE THE PATIENT'S MEDICAL RECORD AND DISCHARGE SUMMARY. ROOT CAUSE: THE AIM SYSTEM DETECTED RBC INTERFACE NEAR TOP OF CHANNEL AND THE CELLS WERE DETECTED IN PLASMA LINE FROM CENTRIFUGE ALARMS CAN BE CAUSED BY A FALSELY LOW PATIENT HEMATOCRIT ENTERED INTO THE SYSTEM. BASED ON THE EVALUATION OF THE PROCEDURE LOG AND THE FACT THAT THE PATIENT WAS RECEIVING RED CELLS; THE LIKELY CAUSE OF

THE ALERTS WAS AN INACCURATELY LOW PATIENT HEMATOCRIT ENTERED INTO THE SYSTEM. BASED ON THE EVALUATION OF THE DEVICE AND RUN DATA FILE; AND THE CUSTOMER STATEMENT REGARDING THE PROCEDURES; THE PATIENT'S DEATH IS UNRELATED TO THE PROCEDURES ON THE SPECTRA OPTIA SYSTEM. Event Description: THE CUSTOMER ORIGINALLY CALLED BECAUSE SHE WAS GETTING AN ALARM 'AIM SYSTEM CANNOT ESTABLISH INTERFACE' DURING A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE. THE PROCEDURE WAS BEING RUN SIMULTANEOUSLY WITH A HEMODIALYSIS PROCEDURE. SHE WAS GETTING RED CELLS DURING THE PROCEDURE AND NOT REMOVING ANY PLASMA AFTER 37 MINUTES. AFTER TROUBLE SHOOTING WITH THE TERUMO BCT SUPPORT SPECIALIST; SHE DECIDED TO SET UP A NEW KIT AND START THE PROCEDURE OVER. SHE WAS ABLE TO FINISH THE PROCEDURE. WHEN THE SUPPORT SPECIALIST CALLED BACK TO COLLECT LOT INFORMATION; THE CUSTOMER INFORMED HER THAT THE PATIENT HAD EXPIRED THE NEXT DAY AFTER THE PROCEDURE ((B)(6) 2013). HEMODIALYSIS AND TRANSFUSIONS WERE BEING DONE AT THE TIME OF HIS DEATH. NO TPE PROCEDURE WAS PERFORMED AT THE TIME OF HIS DEATH. PATIENT IDENTIFIER AND WEIGHT ARE NOT AVAILABLE PER THE MANAGER AT THE CUSTOMER SITE. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN BECAUSE THE CUSTOMER DISCARDED IT. THIS REPORT IS BEING FILED DUE TO PATIENT DEATH (NOT SUSPECTED OF BEING RELATED TO TERUMO BCT DISPOSABLE OR EQUIPMENT BY MEDICAL STAFF). Manufacturer Narrative: INVESTIGATION: THE RUN DATA FILE WAS ANALYZED FOR THIS EVENT. THE SIGNALS IN THE RUN DATA FILE INDICATED THAT THE SPECTRA OPTIA SYSTEM OPERATED AS INTENDED. INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Death#5 (Report# 1722028-2012-00926)

Event Description: ORIGINALLY THE CUSTOMER CALLED THE CLINICAL SUPPORT TEAM TO RECEIVE ASSISTANCE WITH SOME ALARMS THE DEVICE WAS PROVIDING WHILE ATTEMPTING TO START A PROCEDURE. THE CUSTOMER REPORTED THAT THE PATIENT HAD A 14% HEMATOCRIT BEFORE PERFORMING A THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE ON (B)(6) 2012. THE PROCEDURE WAS ENDED EARLY BECAUSE OF THE ALARMS AND PATIENT ISSUES (A CODE TEAM WAS INVOLVED); PER THE CUSTOMER. THE PATIENT THEN RECEIVED A TRANSFUSION OF FIVE UNITS OF BLOOD; AND HER HEMATOCRIT WAS 24% BEFORE THE SECOND ATTEMPT OF THE TPE PROCEDURE WAS STARTED AND COMPLETED ON (B)(6) 2012 (THE SAME DAY). UPON ADDITIONAL FOLLOW-UP WITH THE CUSTOMER; IT WAS DETERMINED THAT THE

PATIENT HAD PASSED AWAY DUE TO HER DISEASE STATE ON (B)(6) 2012; PER THE MEDICAL STAFF. THE CUSTOMER WAS UNABLE TO PROVIDE THE PATIENT IDENTIFIER. THE DISPOSABLE SET IS NOT AVAILABLE FOR RETURN BECAUSE THE CUSTOMER DISCARDED IT. THIS REPORT IS BEING FILED DUE TO THE REPORTED PATIENT DEATH. Manufacturer Narrative: (B)(4). INVESTIGATION: THIS PATIENT WAS IN ICU PRIOR TO THE FIRST TPE PROCEDURE BEING PERFORMED. PER THE MEDICAL STAFF; THE PATIENT DEATH WAS DUE TO HER DISEASE STATE; NOT THE PROCEDURE. PER THE INITIAL DEVICE RUN DATA FILES; THERE WAS NO MALFUNCTION NOTED UPON REVIEW. INVESTIGATION; EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: (B)(4). INVESTIGATION: THE DISPOSABLE SET WAS UNAVAILABLE FOR RETURN AND INVESTIGATION. THE RUN DATA FILE FOR THE FIRST PROCEDURE ON (B)(6) 2012 WAS REVIEWED. THE RUN DATA FILE INDICATES THAT AN AIR BLOCK WAS LIKELY TRAPPED ABOVE THE RBC DETECTOR FOR A PORTION OF THE PROCEDURE AND WAS THE LIKELY CAUSE OF THE ALARMS RECEIVED BY THE OPERATOR. THERE IS NO RISK ASSOCIATED WITH AN AIR BLOCK IN THE SYSTEM. THE DEVICE ALARMED AS INTENDED. THE DEVICE HISTORY RECORD (DHR) WAS REVIEWED FOR THIS LOT. THERE WERE NO ISSUES NOTED IN THE DHR THAT WOULD HAVE CONTRIBUTED TO THIS EVENT. THE LOT MET ALL QUALITY LABS AND STERILIZATION REQUIREMENTS. A REVIEW OF THE LOT FOR SIMILAR REPORTS WAS CARRIED OUT; NONE HAVE BEEN REPORTED. ROOT CAUSE: BASED ON THE DATA LOG ANALYSIS OF THE INITIAL PROCEDURE; THERE WAS AN AIR BLOCK IN THE PLASMA LINE; WHICH CAUSED THE SYSTEM TO ALARM. BASED ON THE INFORMATION PROVIDED BY THE CUSTOMER; THE PATIENT TOLERATED THE PROCEDURE WELL; BUT LATER PASSED AWAY DUE TO THE PROGRESSION OF HER DISEASE STATE.

2011-2012

Death#1 (Report# 1722028-2012-00451)

Event Description: A PATIENT UNDERGOING THERAPEUTIC PLASMA EXCHANGE (TPE) FOR CHRONIC REJECTION POST HEART TRANSPLANT DIED SEVERAL HOURS FOLLOWING A TPE PROCEDURE. THE HOSPITAL INVESTIGATION DETERMINED THAT THE PATIENT'S DEATH WAS COMPLETELY UNRELATED TO THE TPE PROCEDURE. THE CUSTOMER STATED THE PATIENT TOLERATED THE TPE PROCEDURE WELL WITH NO SIDE EFFECTS OR REACTIONS. THE CUSTOMER STATED THEY REPORTED THIS AS A SENTINEL EVENT BECAUSE THE PATIENT DIED WITHIN 24 HOURS OF THE

PROCEDURE. THE CUSTOMER WOULD NOT PROVIDE THE PATIENT IDENTIFIER; AGE; OR WEIGHT CITING HIPAA LIMITATIONS. THE DISPOSABLE SET IS UNAVAILABLE FOR RETURN FOR EVALUATION. THIS REPORT IS BEING FILED DUE TO THE REPORTED PATIENT DEATH. Manufacturer Narrative: (B)(4). INVESTIGATION: THE CUSTOMER STATED THAT THE HOSPITAL PERFORMED AN INVESTIGATION AND DETERMINED THAT THE TPE PROCEDURE WAS RULED OUT AS A CAUSATIVE FACTOR IN THE PATIENT'S DEATH. AN AUTOPSY WAS PERFORMED ON THE PATIENT'S CHEST AND ABDOMEN. THE PATHOLOGIST REPORTED THAT THE CAUSE OF DEATH WAS RELATED TO HEART DISEASE AND WAS NOT RELATED TO THE APHERESIS PROCEDURE. THE CUSTOMER DID NOT PROVIDE A LOT NUMBER; SO A DEVICE HISTORY RECORD SEARCH COULD NOT BE PERFORMED. ALL LOTS MUST MEET ACCEPTANCE CRITERIA FOR RELEASE. ROOT CAUSE: BASED ON THE AUTOPSY RESULTS; THE CAUSE OF DEATH WAS RELATED TO THE PATIENT'S DISEASE STATE AND WAS NOT RELATED TO THE APHERESIS PROCEDURE.

Death#2 (Report# 1722028-2012-00355)

Event Description: THE CUSTOMER REPORTED THAT A PT WAS UNDERGOING THE FIRST THERAPEUTIC PLASMA EXCHANGE (TPE) PROCEDURE FOR NEWLY DIAGNOSED THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP). SHE HAD DIALYSIS THAT MORNING PRIOR TO THE TPE PROCEDURE. HER BLOOD PRESSURE DID DROP TO 89 SYSTOLIC AND THE OPERATOR GAVE HER A BOLUS OF 100 ML OF 0.9% NORMAL SALINE AND INCREASED THE FLUID BALANCE FROM 93% TO 100%. THE PT'S BLOOD PRESSURE CAME UP TO 95 SYSTOLIC AND THEY COMPLETED THE PROCEDURE WITHOUT FURTHER PROBLEMS. THROUGHOUT THE ENTIRE PROCEDURE AND RINSEBACK THE OPERATOR STATES THAT THE PT WAS RESPONSIVE AND DENIED SYMPTOMS RELATED TO CITRATE. THE PT RECEIVED 1 GRAM OF CALCIUM GLUCONATE OVER THE COURSE OF THE PROCEDURE PROPHYLACTICALLY. WHEN THE OPERATOR WAS DISCONNECTING THE PT SHE NOTED THAT THE PT WAS UNRESPONSIVE. SHE PUT THE HEAD OF THE BED DOWN; CONTACTED THE PT'S PRIMARY NURSE AND THE PHYSICIAN AS SHE WAS NOT ABLE TO FIND A PULSE ON THE PT. CPR WAS INITIATED AND THE PT WAS GIVEN MEDICATIONS PER THE CODE TEAM. THE OPERATOR DID NOT KNOW WHAT MEDICATIONS WERE GIVEN. SHE DID NOTE THAT DURING THE RESUSCITATION EFFORTS THE PT WAS HAVING PROFUSE BLEEDING FROM THE MOUTH AND NOSE. AFTER 25 MINUTES OF RESUSCITATION THE PT DIED. IT IS UNK AT THIS TIME IF THE DEATH WAS PROCEDURE/PRODUCT-RELATED. TERUMO BCT IS AWAITING AUTOPSY RESULTS OF THE PT. THE DISPOSABLE SET IS UNAVAILABLE FOR RETURN BECAUSE THE CUSTOMER

DISCARDED THE KIT. THIS REPORT IS BEING FILED DUE TO A PT DEATH. Manufacturer Narrative: (B)(4). INVESTIGATION: THE OPERATOR DETERMINED THAT DURING DIALYSIS PROCEDURES THIS PT'S BLOOD PRESSURE NORMALLY RUNS BETWEEN 85 AND 100 SYSTOLIC; AND THEY CONSIDER IT LOW IF THE SYSTOLIC DROPS BELOW 70. A SERVICE CALL WAS PLACED FOR THE EQUIPMENT. NO PROBLEMS WERE FOUND DURING CHECK OUT OF THE MACHINE. INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED. Manufacturer Narrative: (B)(4). THIS REPORT IS BEING FILED TO PROVIDE ADDITIONAL INFORMATION. INVESTIGATION: THE DEVICE HISTORY RECORD WAS REVIEWED. NOTHING WAS FOUND THAT WAS RELATED TO THIS EVENT. THE OPERATOR STATED THAT THERE WAS ONE PLASMA LINE CONTAMINATION MESSAGE DURING THE PROCEDURE. SHE INCREASED THE HEMATOCRIT BY 3% AND THE RED BLOOD CELLS IN THE PLASMA LINE CLEARED. THE CBC DRAWN ON THE PATIENT WAS PRE-DIALYSIS; SO THE HEMATOCRIT USED MAY NOT HAVE BEEN FULLY ACCURATE. A SERVICE CALL WAS PLACED ON THE DEVICE. NO ISSUES WERE FOUND AND THE MACHINE WAS FUNCTIONING AS INTENDED. THE CUSTOMER PERFORMED THEIR OWN INTERNAL INVESTIGATION AND DETERMINED THAT THE CAUSE OF THE DEATH WAS DUE TO THE PATIENT'S UNDERLYING DISEASE STATE. A STATEMENT ABOUT THE CAUSE OF DEATH COULD NOT BE OBTAINED FROM THE HOSPITAL. ROOT CAUSE: BASED ON THE CUSTOMER'S INTERNAL INVESTIGATION; THE PATIENT'S UNDERLYING DISEASE STATE WAS THE CAUSE OF DEATH. Manufacturer Narrative: (B)(4). THIS REPORT IS BEING FILED TO PROVIDE ADDITIONAL INFORMATION. IN A CONVERSATION WITH THE PATIENT'S DOCTOR; IT WAS DETERMINED THAT THE PATIENT; PRIOR TO THE TPE; HAD WORSENING OF CARDIO AND RENAL STATUS; HAD A HISTORY OF CONGESTIVE HEART FAILURE AND WAS A HIGH MEDICAL RISK PATIENT IN GENERAL. SHE WAS NOT RESPONDING TO OTHER TREATMENTS (IE: STEROIDS) AND HER PLATELET COUNT WAS DROPPING. THE MEDICAL STAFF BEGAN TO SUSPECT THAT SHE HAD TTP. SHE WAS ALSO EXPERIENCING MENTAL STATUS CHANGES ALONG WITH THE PLATELET COUNT DROP; SO A TPE PROCEDURE WAS ORDERED. IN A CONVERSATION WITH THE PATIENT'S SURGEON; HE DID NOT FEEL THAT THE TPE WOULD HAVE BEEN RELATED TO THE PATIENT'S DEATH; BUT RECOMMENDED CONTACTING THE HEMATOLOGIST / ONCOLOGIST / NEPHROLOGIST FOR THIS PATIENT TO CONFIRM. MULTIPLE ATTEMPTS TO GET INTO CONTACT WITH THIS PHYSICIAN HAVE BEEN UNSUCCESSFUL AT THIS TIME. IF FURTHER INFORMATION IS RECEIVED FROM THIS PHYSICIAN; FOLLOW-UP INFORMATION WILL BE PROVIDED. NO AUTOPSY WAS PERFORMED ON THIS PATIENT.

Death#3 (Report# 1722028-2011-00414)

Event Description: A CARIDIANBCT EMPLOYEE READ THE ARTICLE ON PLATELET BACTERIAL CONTAMINATION IN THE (B)(6); PUBLISHED ON (B)(6) 2011. A PT DEATH WAS INVOLVED. AT THIS TIME THERE IS INSUFFICIENT INFO PROVIDED TO DETERMINE IF A CARIDIANBCT DEVICE WAS INVOLVED. SEVERAL ATTEMPTS HAVE BEEN MADE TO CONTACT THE SITE WITH NO RESPONSE. THE PT INFO IS UNAVAILABLE AT THIS TIME. THE DISPOSABLE IS UNAVAILABLE FOR EVAL BECAUSE IT WAS DISCARDED. THIS REPORT IS BEING FILED DUE TO INSUFFICIENT INFO PROVIDED AT THIS TIME TO DETERMINE IF OUR DEVICE WAS INVOLVED IN A DONOR PT DEATH. Manufacturer Narrative: (B)(4). (B)(6). THE PTS RECEIVED PLATELETS ON (B)(4) 2011. THE RUN DATA FILES FOR THESE MACHINES USED AT THIS SITE WERE UPLOADED TO CARIDIANBCT: MACHINE# (B)(4): FILES INDICATE NO COLLECTIONS BETWEEN THE DATES OF (B)(6). MACHINE# (B)(4): FILES INDICATE NO COLLECTION BETWEEN THE DATES OF (B)(6). INVESTIGATION EVAL AND CORRECTIVE ACTIONS ARE IN PROGRESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

Death#4 (Report# 1722028-2011-00462)

Event Description: A CARIDIANBCT EMPLOYEE READ THE ARTICLE ON PLATELET BACTERIAL CONTAMINATION IN (B)(6); PUBLISHED ON (B)(6) 2011. A PT DEATH WAS INVOLVED. AT THIS TIME THERE IS INSUFFICIENT INFO PROVIDED TO DETERMINE IF THE CARIDIANBCT DEVICE WAS INVOLVED. SEVERAL ATTEMPTS HAVE BEEN MADE TO CONTACT THE SITE WITH NO RESPONSE. THE PT INFO IS UNAVAILABLE AT THIS TIME. THE DISPOSABLE IS UNAVAILABLE FOR EVAL BECAUSE IT WAS DISCARDED. THIS REPORT IS BEING FILED DUE TO INSUFFICIENT INFO PROVIDED AT THIS TIME TO DETERMINE IF OUR DEVICE WAS INVOLVED IN A DONOR/PT DEATH. Manufacturer Narrative: (B)(4). (B)(6). THE PTS RECEIVED PLATELETS ON (B)(6) 2011. THE RUN DATA FILES FOR THESE MACHINES USED AT THIS SITE WERE UPLOADED TO CARIDIANBCT: MACHINE# (B)(4): FILES INDICATE NO COLLECTIONS BETWEEN THE DATES OF (B)(6). MACHINE# (B)(4): FILES INDICATE NO COLLECTIONS BETWEEN THE DATES OF (B)(6). INVESTIGATION; EVALUATION AND CORRECTIVE ACTIONS ARE IN PROGRESS. A FOLLOW-UP REPORT WILL BE PROVIDED.

2010-2011

Death#1 (Report# 1722028-2011-00098)

Event Description: DURING PRIME; THE CUSTOMER RECEIVED A 'WASTE VALVE NOT OPERATING CORRECTLY' ALARM. THE CUSTOMER CHANGED THE KIT AND STARTED THE PRIMING OVER. LATER; (B)(4) BECAME AWARE THAT THE (B)(6) PT HAD PASSED AWAY THE NEXT MORNING PRIOR TO MAKING IT INTO EMERGENCY LIVER TRANSPLANT SURGERY. Manufacturer Narrative: (B)(4). INVESTIGATION EVALUATION AND CORRECTIVE ACTIONS ARE IN-PROCESS. A FOLLOW-UP REPORT WILL BE PROVIDED.