



# Classification of Centrifuge-Type Therapeutic Apheresis Devices under Product Code “LKN”

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# Centrifuge-Type Therapeutic Apheresis Devices (LKN)

- Designed to separate plasma or blood components from whole blood.
- Regulated under product code “LKN” as “Separator, automated, blood cell and plasma, therapeutic.”
- 17 clearances for centrifuge devices for therapeutic blood cell or plasma exchange and 2 clearances for accessories (plasma discard bags).

## Notes:

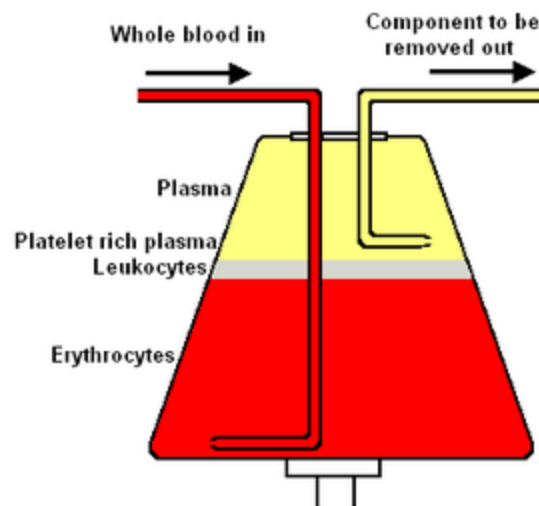
- This product code only includes the *therapeutic* use of centrifuge-type apheresis equipment (does not include use of centrifuge apheresis indications for blood donation).
- This product code does not apply to membrane-type apheresis devices.

## Device Description

- Centrifuge-type therapeutic apheresis devices are designed to separate plasma or blood components from whole blood, for the purposes of depletion or exchange of these components or plasma.
- These devices are typically automated continuous-flow systems that are comprised of a:
  - » Blood component separator instrument
  - » Disposable apheresis kit

## Device Description

- The blood component separator draws whole blood from a patient and separates the blood into its components, utilizing centrifugal force as the basis of operation.
- The system collects one or more of the blood components, and returns the remainder of the blood components to the patient.



## Indications for Use

Representative indications for use statements are:

- 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.

## Indications for Use

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.

## Adverse Events and Risks

- Manufacturer and User facility Device Experience (MAUDE) database (September 2010 to August 2015)
- Information available to FDA regarding cleared devices
- Review of literature on PubMed (January 1980 to September 2014) using representative key terms.
- Recall search (September 2010 to August 2015)

## Adverse Events and Risks (cont'd)

- Searches of the MAUDE database returned 1447 Medical Device Reports (MDRs) from September 1, 2010, to August 31, 2015.
- Of note, several of the above MDRs pertain to devices not for this indication (i.e. blood donation procedures).
- 8 Recalls (3 different apheresis systems)
  - » Greater than anticipated red blood cell removal, issues with air detection, excess loss of platelets, software corrections to improve usability, and labeling corrections.



## Adverse Events and Risks (cont'd)

The reported adverse events fall into the following categories:

Dates of Search	Total MDRs	Deaths	Injury	Malfunction	Other / NA
Sep 2010 to Aug 2011	425	1	46*	107	271
Sep 2011 to Aug 2012	489	4	2	329	156
Sep 2012 to Aug 2013	113	5	3	29	81
Sep 2013 to Aug 2014	130	5	3	0	102
Sep 2014 to Aug 2015	290	6	2	202	86

\* 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 evaluation process that were prompted by an FDA inspection.”

## Adverse Events and Risks (cont'd)

- Literature Review
  - » 32 articles with relevant information
    - Centrifuge devices marketed in US
    - Clinical studies conducted in humans
    - Safety and Effectiveness of Therapeutic Apheresis
  - » Safety Conclusions:
    - Adverse events (AE) are well-described:
      - e.g., hypotension/hypovolemia, symptomatic hypocalcemia, allergic reactions
    - Events are typically non-serious and resolve without clinical consequences

## Risks to Health

- Thrombosis in patient and device
- Adverse tissue reaction
- Infection and pyrogen reactions
- Device failure / Disposable failure
- Air embolism
- Hemolysis
- Blood loss/Anemia
- Toxic reaction to anticoagulant
- Electrical shock hazard
- Fluid imbalance
- Inadequate separation of blood components
- Operator error

## Risks and Mitigations

Identified Risk	Description/ Examples	Recommended Mitigation Measures
<p><b>Thrombosis in patient and device</b></p>	<p>This can include clotting of the extracorporeal circuit, vascular access clotting, or clotting of other blood vessels.</p>	<p>Performance testing Sterility Labeling Clinical performance testing</p>
<p><b>Adverse tissue reaction</b></p>	<p>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 or reactions to blood products used with the device.</p>	<p>Biocompatibility Sterility Expiration date testing Labeling</p>
<p><b>Infection and pyrogen reactions</b></p>	<p>This risk includes febrile reactions, inflammatory response syndromes, infection, sepsis, and microbial contamination.</p>	<p>Performance testing Sterility Expiration date testing Labeling</p>

## Risks and Mitigations (cont'd)

Identified Risk	Description/ Examples	Recommended Mitigation Measures
<b>Device failure / Disposables failure</b>	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)	Performance testing Expiration date testing Labeling
<b>Air embolism</b>	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.	Performance testing Labeling
<b>Hemolysis</b>	This risk includes damage to red blood cells with subsequent release of cellular contents resulting from the mechanical processing of blood.	Performance testing Labeling

## Risks and Mitigations (cont'd)

Identified Risk	Description/ Examples	Recommended Mitigation Measures
<p><b>Blood loss / Anemia</b></p>	<p>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.</p>	<p>Performance testing Labeling</p>
<p><b>Toxic reaction to anticoagulant</b></p>	<p>This can include citrate toxicity, which is typically manifested by hypocalcemia (paresthesia, tetany, seizures, and cardiac arrhythmias) and alkalosis.</p>	<p>Performance testing Labeling Clinical performance testing</p>
<p><b>Electrical shock hazard</b></p>	<p>This risk can include electrical burns and cardiac arrhythmias.</p>	<p>Performance testing Labeling</p>

## Risks and Mitigations (cont'd)

Identified Risk	Description/ Examples	Recommended Mitigation Measures
<b>Fluid imbalance</b>	This risk can result in hypovolemia (e.g., hypotension, headache, nausea/vomiting, syncope) or fluid overload (e.g., hypertension, pulmonary congestion).	Performance testing Labeling Clinical performance testing
<b>Inadequate separation of blood components</b>	This risk involves the unintended removal of blood components (e.g., loss of immunoglobulins, drugs, electrolytes, coagulation factors, etc.).	Performance testing Clinical performance testing
<b>Operator error</b>	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).	Performance testing (usability) Labeling

## Proposed Classification Regulation

### **876.XXXX Centrifuge-Type Therapeutic Apheresis Device** (or therapeutic automated blood cell and plasma separator, centrifuge-type)

(a) *Identification.* 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:



## Proposed Classification Regulation (cont'd)

- 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).

# Proposed Classification Regulation (cont'd)

**876.XXXX Centrifuge-Type Therapeutic Apheresis Device** (or therapeutic automated blood cell and plasma separator, centrifuge-type)

(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.

## Proposed Classification Regulation (cont'd)

- 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;

## Proposed Classification Regulation (cont'd)

- 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 data must demonstrate sterility of the device; and
- viii. Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life.

## Proposed Classification Regulation (cont'd)

### 3) Labeling must include the following:

- i. A description of the device and individual 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;

## Proposed Classification Regulation (cont'd)

- 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.

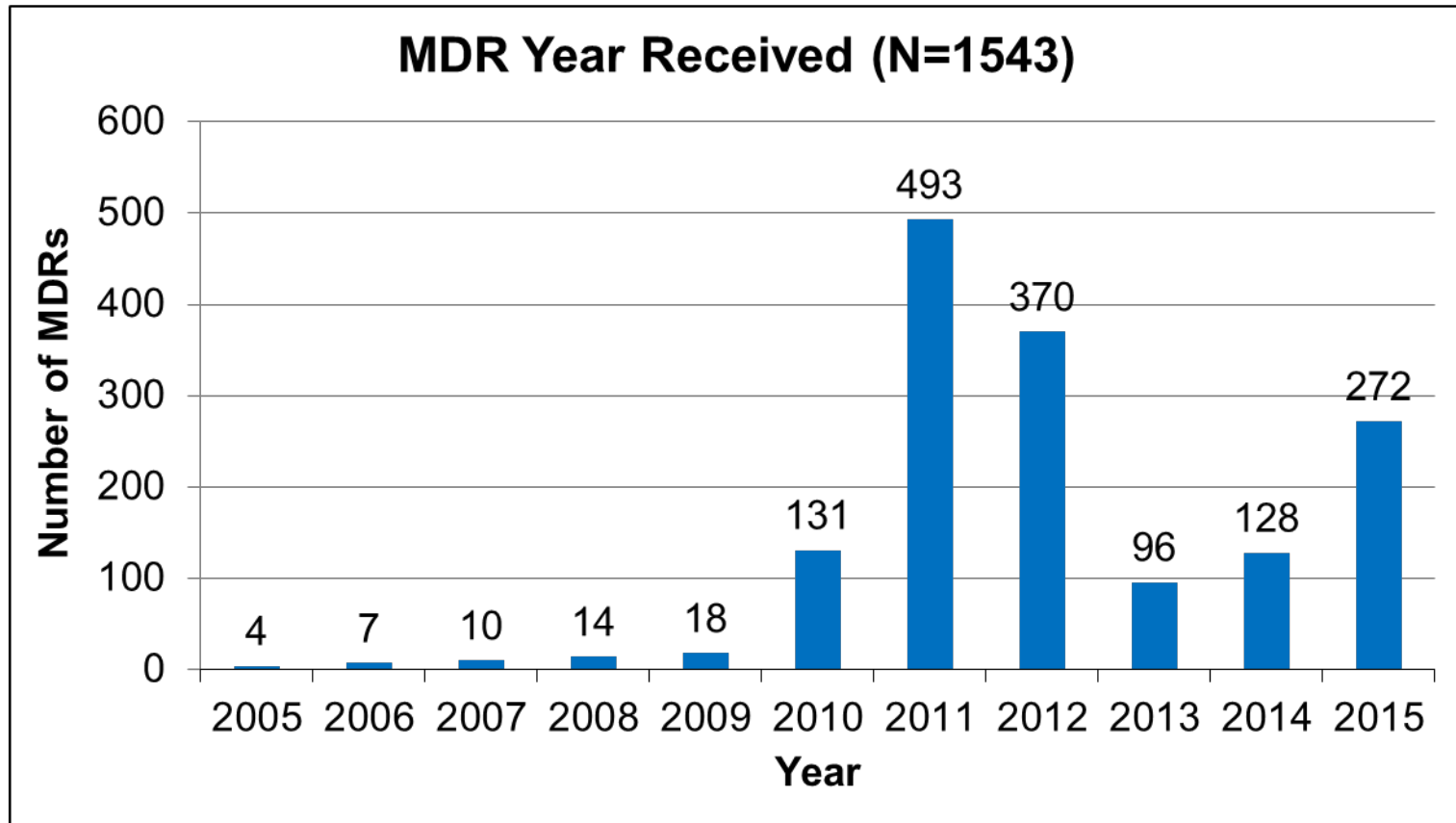




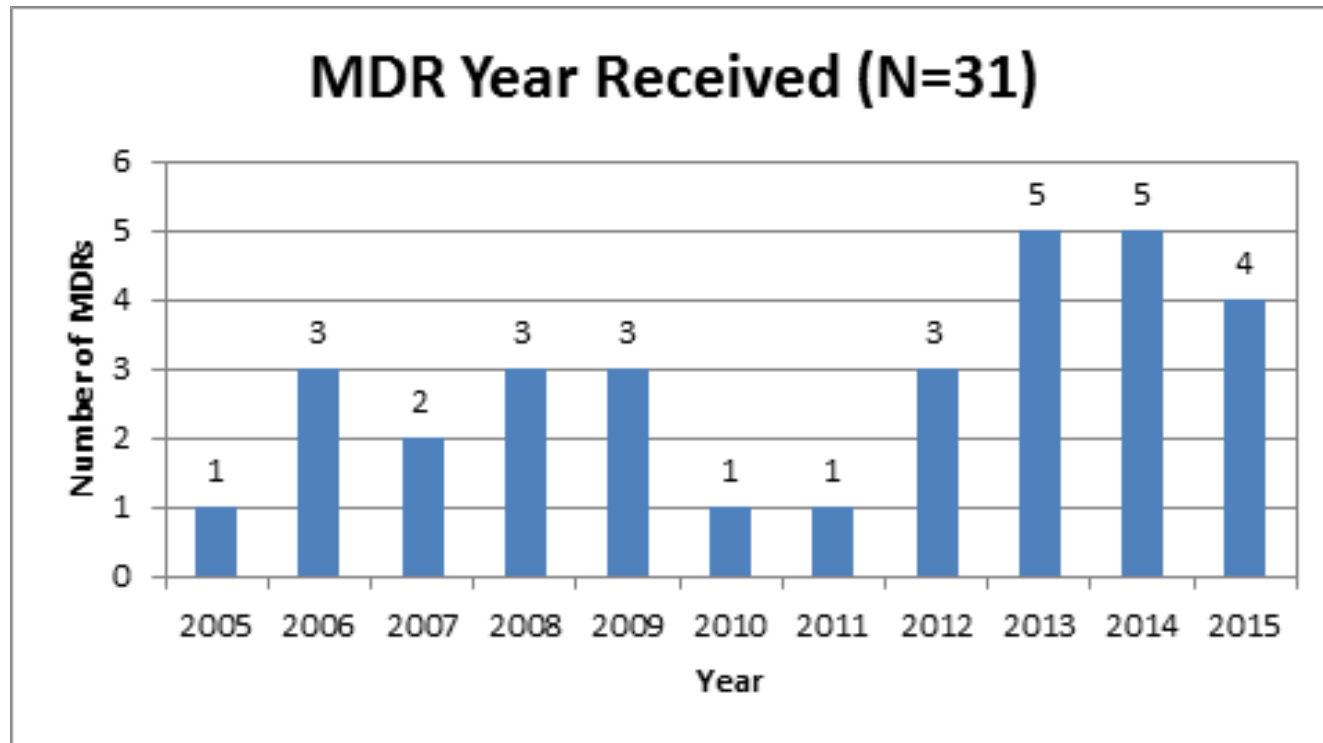
# Extra Slides



# LKN MDRs (2005 to 2015)







# MDR Death Results (2005 to 2015)



**Our analysis of the results since 2005 revealed the deaths were not attributable to the device.**



# MDR Reporting Requirements

REPORTER	WHAT TO REPORT	WHERE	WHEN
<b>Manufacturer (Mfr)</b> 	<b>Deaths, Serious Injuries, Malfunction</b>	<b>FDA</b>	<b>Within 30 calendar days of becoming aware</b>
<b>User Facility</b> 	<b>Deaths</b>	<b>FDA and Mfr</b>	<b>Within 10 working days</b>
	<b>Serious Injury</b>	<b>Mfr (FDA if unknown)</b>	<b>Within 10 working days</b>
<b>Importer</b> 	<b>Deaths and Serious Injuries</b>	<b>FDA and Mfr</b>	<b>Within 30 calendar days</b>
	<b>Malfunctions</b>	<b>Mfr</b>	<b>Within 30 calendar days</b>
<b>Voluntary</b> 	<b>Any type of event</b>	<b>FDA</b>	<b>Any time</b>

# Limitations and Uses of MDRs

- Limitations
  - » Under-reporting of events
  - » Inadequate or insufficient information
  - » Inability to establish causality
  - » Inability to calculate a “rate” of event
  - » Difficulty in assessing trends
  
- Uses
  - » Qualitative snapshot of real-world AEs for a device/device type
    - Types and severities of malfunctions and/or clinical events
    - Clinical sequelae and treatments required to address issue
  - » Monitor device performance/Signal detection
    - Unexpected events
    - Change in severity or outcomes of expected events
    - User error/human factors issues

# Medical Device Reporting (MDR)

- FDA receives several 100K Medical Device Reports (MDRs) annually (suspected device-associated deaths, serious injuries and malfunctions).
- Medical Device Reporting is one of FDA's postmarket surveillance tools to monitor device performance, detect device-related safety issues, and contribute to benefit-risk assessments.
- Mandatory reporters (i.e., manufacturers, device user facilities, and importers) are required to submit certain types of reports for adverse events and product problems to FDA about medical devices.
- FDA also encourages health care professionals, patients, caregivers and consumers to submit voluntary reports about serious adverse events that may be associated with a medical device, as well as use errors, product quality issues, and therapeutic failures.
- These reports, along with data from other sources, can provide critical information that helps improve patient safety.

# MAUDE Database

- The Manufacturer and User Facility Device Experience (MAUDE) database houses MDRs submitted to the FDA by:
  - » mandatory reporters (manufacturers, importers and device user facilities); and
  - » voluntary reporters (health care professionals, patients and consumers).
- The MAUDE database contains:
  - » mandatory reports filed by manufacturers and importers from August 1996 to present;
  - » all mandatory user facility reports from 1991 to present; and
  - » voluntary reports filed after June 1993.

## Literature Review

- Literature Search Terms on PubMed (January 1980 to September 2014):
  - » (“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 Plasmfiltration 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.”)

## Literature Review

- Literature Search (January 1980 to September 2014):
- 1215 articles
  - » 978 excluded based on abstract (non-clinical, case report, non-English, non-human, no abstract, no endpoints, non-systematic review, sample size <10)
  - » 205 excluded after full text review (device not specified, device not approved in US, membrane apheresis devices, etc.)
  - » 32 articles included (Majority of reports were for TPE)



# Literature Review

- Adverse events noted:
  - » Hypotension
  - » Allergic reactions
  - » Nausea/vomiting
  - » Headache
  - » Fatigue
  - » Paresthesia
  - » Arrhythmia
  - » Infection
  - » Bleeding
  - » Abnormalities in blood counts
  - » Electrolyte changes

## Recall Classifications

- **A Class I recall is a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.**
- **A Class II recall is a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.**
- **A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.**