

Classification of Centrifuge-Type Therapeutic Apheresis Devices FDA Questions

**Gastroenterology and Urology Devices Panel of Medical Devices Advisory Committee
February 26, 2016**

1. FDA has identified the following risks to health for 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).

Please comment on whether you agree with inclusion of all of the risks in the overall risk assessment of the centrifuge-type therapeutic apheresis devices. In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of centrifuge-type therapeutic apheresis devices.

2. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:
- insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, 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.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR

- insufficient information exists to:
 - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
 - establish special controls to provide such assurance, BUT
 - I. is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, AND
 - II. does not present a potential unreasonable risk of illness or injury.

FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that Class II is the appropriate classification for centrifuge-type therapeutic apheresis devices. 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.

Risk/mitigation recommendations for the 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
Air embolism	Performance testing Labeling
Hemolysis	Performance testing Labeling
Blood loss / anemia	Performance testing Labeling

Identified Risk	Recommended Mitigation Measures
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

Please discuss whether the following proposed special controls for centrifuge-type therapeutic apheresis devices appropriately mitigate the identified risks to health and whether additional or different special controls are recommended:

- a. The patient-contacting components of the device must be demonstrated to be biocompatible;
- b. Performance data must demonstrate that the device performs as intended under anticipated conditions of use as follows:
 - o 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;
 - o mechanical hemolysis testing must be conducted;
 - o a system-level hazard analysis must confirm that the device does not perform in an unexpected and/or unsafe manner;
 - o software verification and validation testing must be performed;
 - o appropriate analysis and non-clinical testing must be conducted to validate electrical safety;
 - o appropriate analysis and non-clinical testing must be conducted to validate electromagnetic compatibility (EMC);
 - o performance data must demonstrate sterility of the device;
 - o performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life;
- c. Labeling must include the following:
 - o 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
- d. 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.

3. Please discuss whether you agree with FDA's proposed classification of Class II with special controls for centrifuge-type therapeutic apheresis devices. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.