Bristol Myers Squibb®

CAR T ACADEMY

Apheresis

CAR T Academy: Apheresis

01: PROCEDURE OVERVIEW

02: COLLECTION CONSIDERATIONS

03: TECHNICAL CONSIDERATIONS

04: SCHEDULING AND SHIPPING

Journey Through the CAR T Cell Therapy Process

Icon indicates areas of collaboration between the non-CAR T and CAR T treatment teams

Manufacturing

Patient identification[1,2]

- Appropriate patients are identified for treatment at qualified treatment sites or referring sites
- Early collaboration may facilitate timely referral and eligibility evaluation
- Once a patient is confirmed as eligible, leukapheresis is scheduled

Apheresis[1-4]

- Before apheresis, patients undergo a washout of prior medications that may affect T cell health to ensure optimal collection
- Physicians, APPs, and nurse coordinators all play a role in ensuring a proper washout occurs before apheresis
- Patients then undergo apheresis, which involves collection of white blood cells
- The collected apheresis product is then sent to the manufacturer

Bridging[1,3]

- Bridging therapy may be given to maintain disease control during CAR T cell manufacturing
- Appropriate bridging therapy should be discussed and coordinated between the referring physicians and those treating with CAR T cell therapy

LDC and Infusion[1-3]

- LDC is administered prior to CAR T cell infusion to deplete endogenous T cells and create an environment for CAR T cell expansion
- Infusion will then occur at the qualified treatment center

Monitoring and long-term follow-up[1,2,5]

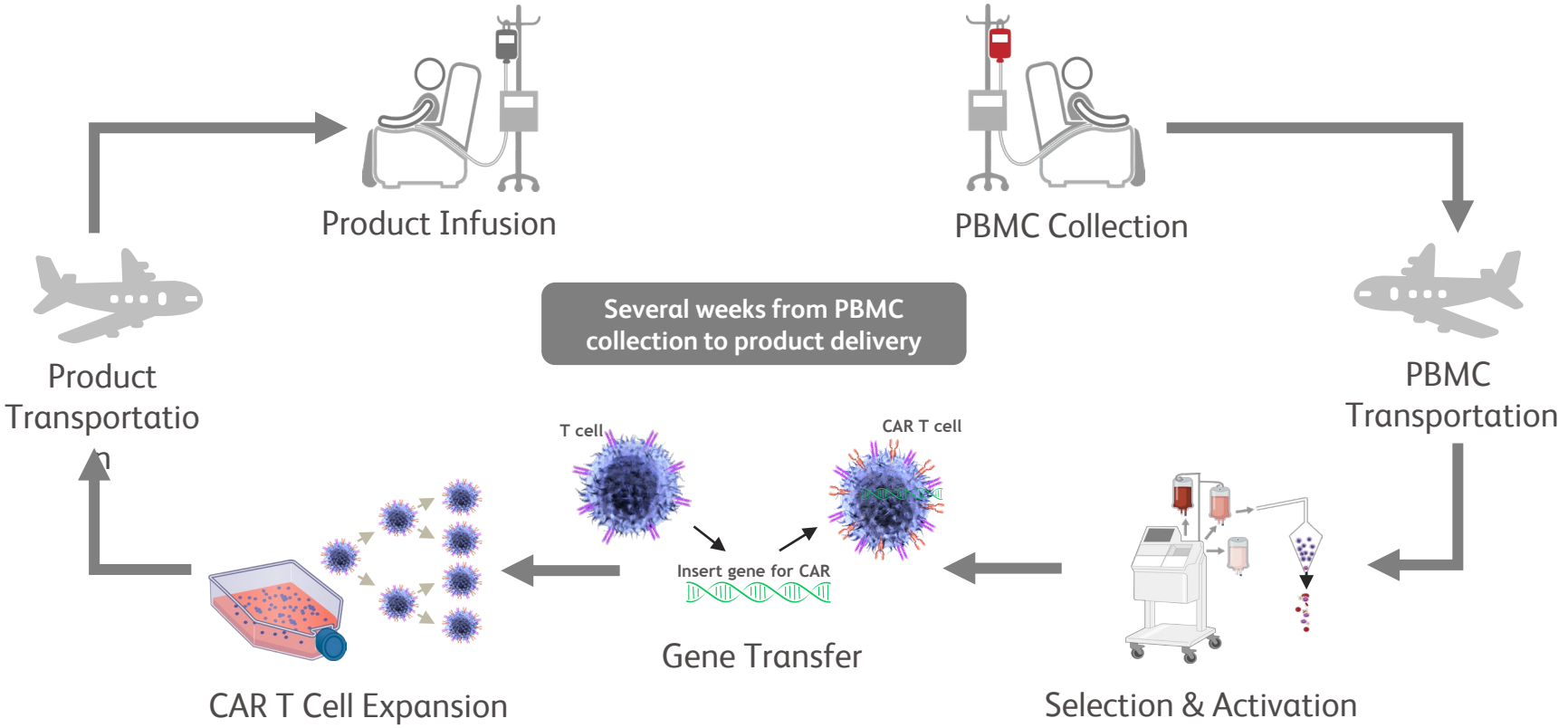
- After infusion, patients are closely monitored for at least 2 weeks at the CAR T cell therapy treatment site, and side effects are promptly managed
- After at least 2 weeks, patients may be discharged back to the referring physician's care
- Communication continues between the CAR T cell therapy treatment center and the primary hematologist/ oncologist as patients are monitored long-term

APP, advanced practice provider; CAR, chimeric antigen receptor; LDC, lymphodepleting chemotherapy.

References: 1. Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **3.** McGuirk J, et al. *Cytotherapy*. 2017;19(9):1015-1024. **4.** Qayed M, et al. *Cytotherapy*. 2022;S1465-3249(22)00641-7. **5.** US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor

Importance of Apheresis

Apheresis is a critical step in the autologous CAR T cell manufacturing process in which the starting material used to produce the CAR T cell therapy is collected[1,2]



The manufacturing process cannot begin without successful collection of the patient's white blood cells

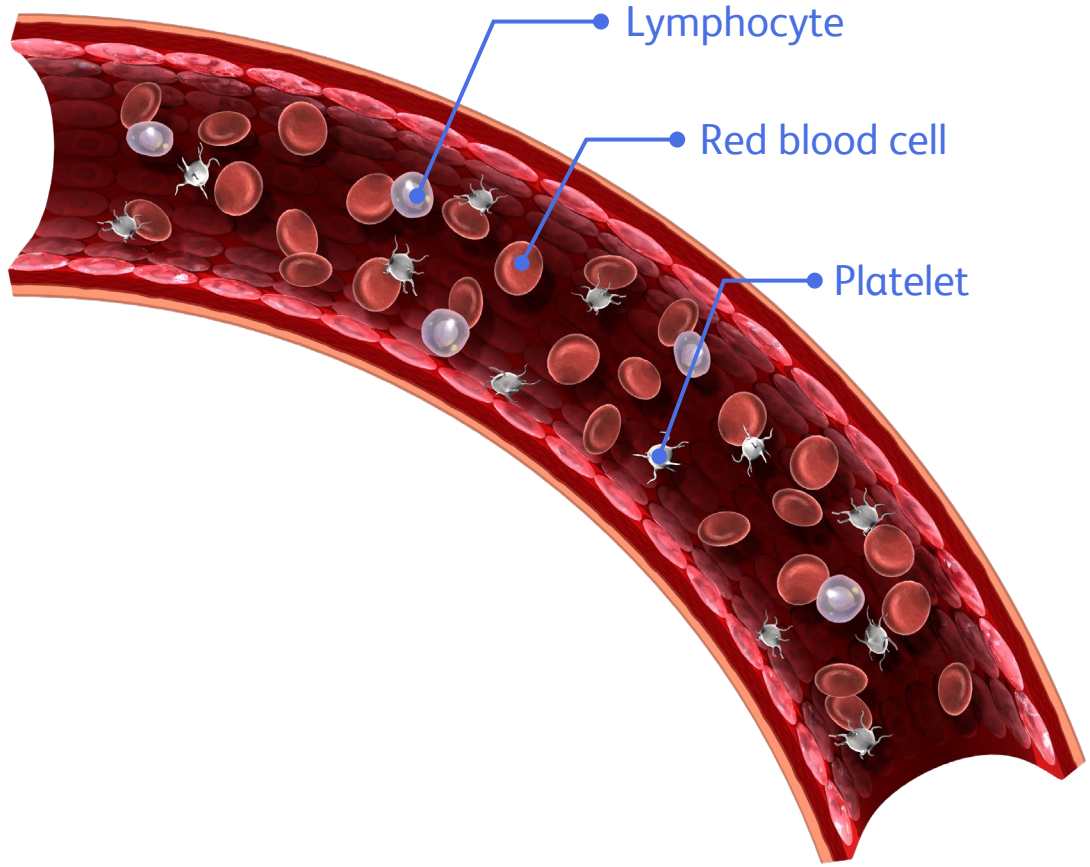
PBMC, peripheral blood mononuclear cell.

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **2.** McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024.

Apheresis

Greek word root: “to take away”

- Apheresis begins with whole blood removal
- Blood is separated into different layers by centrifugation using specific gravity of cellular components (plasma, platelets, leukocytes, erythrocytes)
- Certain cellular components or plasma can be removed, replaced, or treated in-line and returned
- Remaining blood components are returned to the body



Reference: Chegini A, et al. *Transfus Apher Sci.* 2019;58(3):266-272.

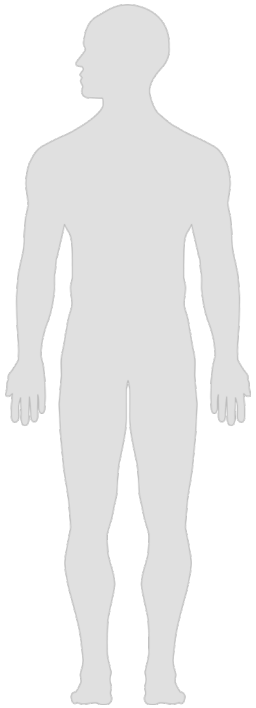
Types of Apheresis

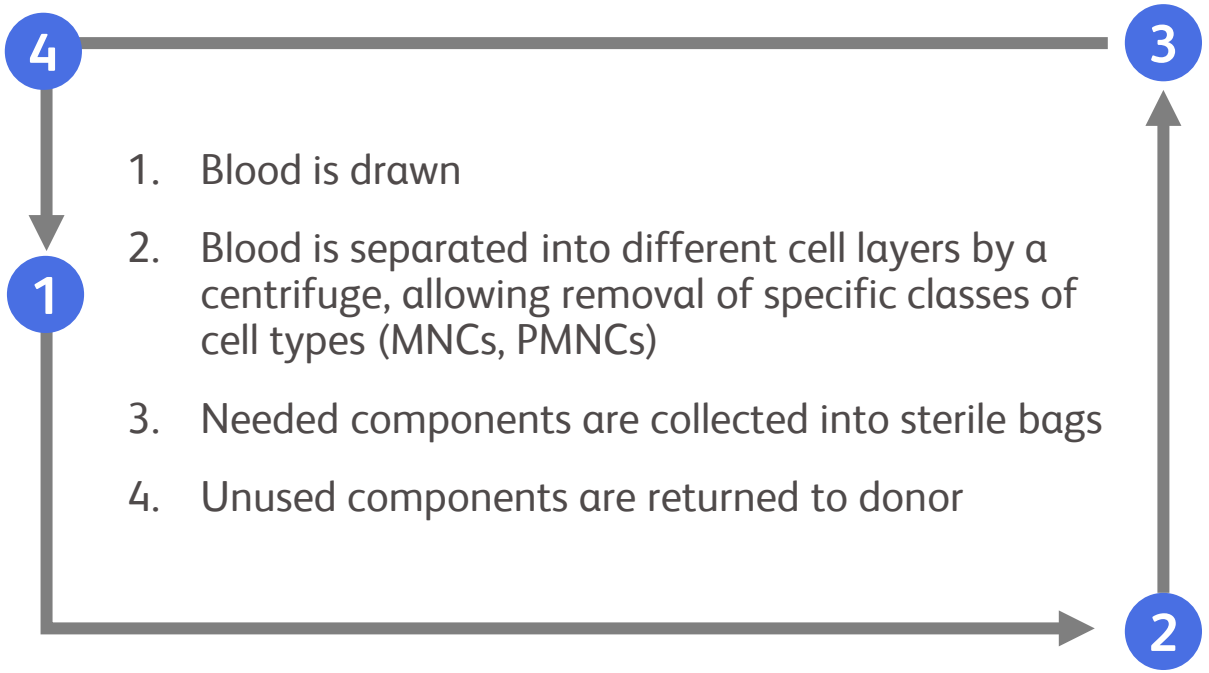
Type of Apheresis	Examples
Therapeutic Apheresis[1,2]	• Plasma exchange (eg, for thrombotic thrombocytopenic purpura, Guillain-Barre Syndrome, myasthenia gravis) • Red blood cell exchange (eg, for sickle cell disease) • White blood cell depletion (eg, for select leukemias) • Platelet depletion • Low-density lipoprotein (LDL) apheresis • Photopheresis
Collection Apheresis[1]	• Platelets • Plasma • Red blood cells • **White blood cells** ← **Collection of white blood cells from the peripheral blood is called leukapheresis**[1]

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Szczepiorkowski ZM, et al. *J Clin Apher*. 2010;25(3):83-177.

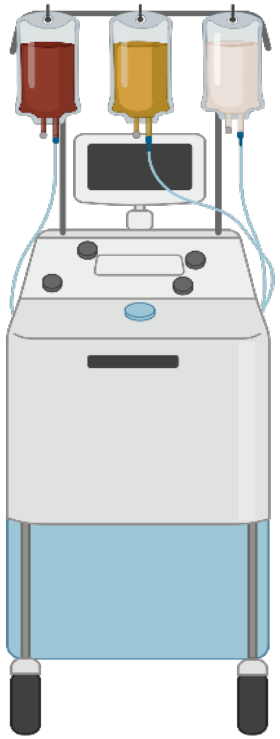
Apheresis Process

The apheresis process requires appropriate and approved collection devices, adherence to good clinical practice requirements and product-specific protocols, as well as trained personnel[1-3]





1. Blood is drawn
2. Blood is separated into different cell layers by a centrifuge, allowing removal of specific classes of cell types (MNCs, PMNCs)
3. Needed components are collected into sterile bags
4. Unused components are returned to donor

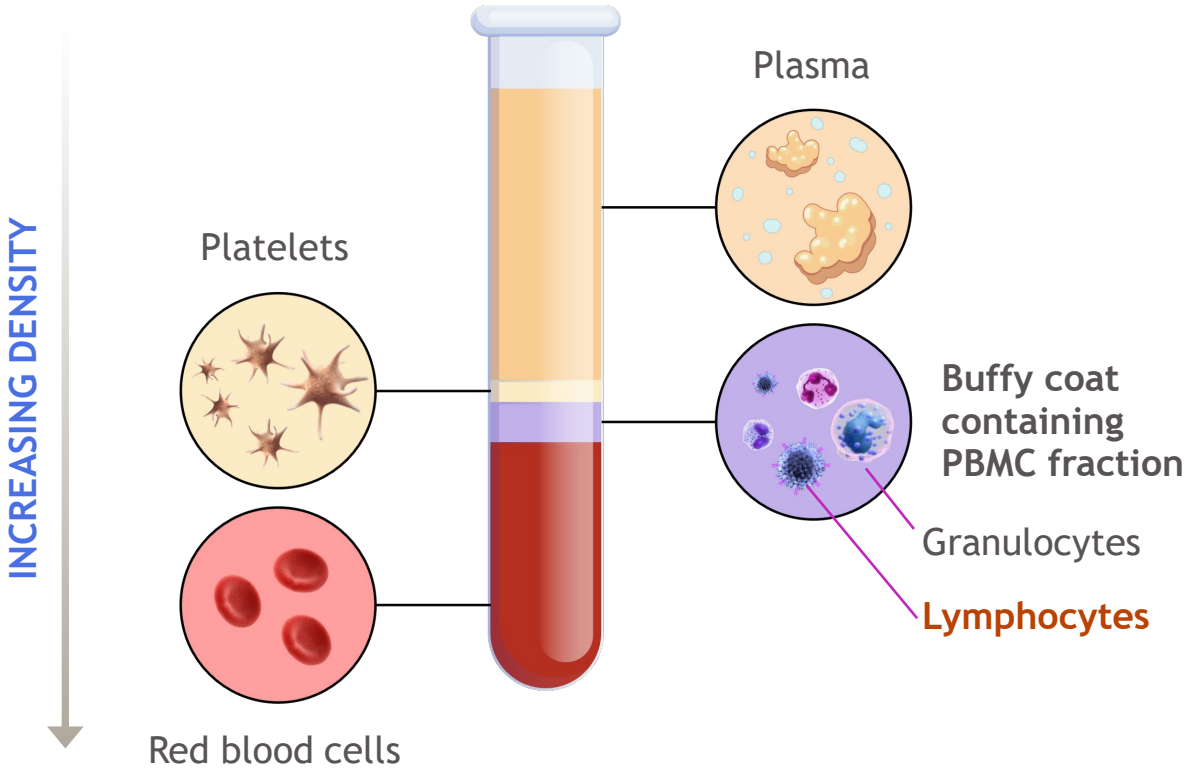


MNC, mononuclear cell; PMNC, polymorphonuclear cell.

References: 1. Perica K, et al. *Biol Blood Marrow Transplant.* 2018;24:1135-1141. **2.** McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **3.** Fesnak A, et al. *Transfus Med Rev*. 2016;30:139-145.

Leukapheresis

Separation of Blood Components for CAR T Cell Therapy[2]



- The apheresis process separates out general classes of cells, such as MNCs, PMNCs (polymorphonuclear cells), or blood components like plasma
- MNCs are located in the buffy coat which consists of lymphocytes + monocytes, PMNCs, and platelets. Red cells are the heaviest and will pack in the very bottom layer
- After apheresis, additional steps to isolate specific types of leukocytes (eg, T cells) are carried out in a cell processing laboratory

MNC, mononuclear cell; PMNC, polymorphonuclear cell.

Reference: Fesnak A, et al. *Transfus Med Rev*. 2016;30:139-145.

Apheresis: Possible Adverse Events

In a retrospective analysis of

15,763

apheresis procedures

at a single center (2006–2009)[1]:

The incidence of moderate/severe AEs was

0.37%

Possible AEs[2]:

- Fatigue
- Nausea
- Dizziness
- Chills
- Tingling/paresthesia (fingers, mouth)

Rare AEs[1,2]:

- Abnormal heart rate
- Seizures
- Rash
- Burn (from heat pack application)
- Vascular access sequelae (eg, hematomas, nerve injuries after venipuncture)

AE, adverse events.

References: 1. Yuan S, et al. *Transfusion*. 2010;50:478-486. **2.** Maus MV, Levine BL. *Oncologist*. 2016;21:608-617.

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Considerations Prior to Leukapheresis

Assessments will determine the plan of care:

History and physical

- *Can the patient withstand the procedure?*
- *Are there any significant comorbidities?*

➢ Important to verify prior to initiating leukapheresis

Laboratory values[1,2]

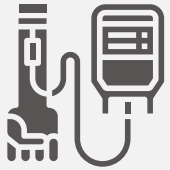
- *Does the patient have sufficient red blood cells, platelets, and white blood cells to begin the procedure?*

➢ Ensure that sufficient cells can be collected
➢ Reduce risk of possible complications (eg, syncope, bleeding)

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Considerations Prior to Leukapheresis (cont.)

Assessments will determine the plan of care:



Venous assessment[2]

- *Is there adequate venous access?*
- *Can peripheral veins be used or is there a need to place a central venous catheter?*

➢ In some cases, it may be necessary to place a temporary or permanent dialysis-grade catheter in pediatric patients or a central venous catheter in adolescent and adult patients[2]

Treatment history[1,2]

- *Has the patient undergone stem cell transplantation (SCT) within 3 months?*
- *Are there other concomitant medications that might lead to low blood counts and/or complications?*

➢ Leukapheresis is discouraged within 3 months of allogeneic SCT due to the risk for graft-versus-host disease (GVHD)[2]

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Patient Education

The apheresis unit will counsel patients and provide instructions regarding the procedure, such as the following:

Pre-collection

Eat prior to the procedure, especially calcium-rich foods[1]

Increase fluid intake for 2 days, but limit fluids for 3 hours immediately before[2]

Hold certain medications prior to treatment, following HCP recommendations[3]

Bring entertainment![1]

Post-collection

Limit activity for 12 hours – mild fatigue or dizziness may occur. Contact your physician if you experience dizziness[4]

Continue to drink fluids to stay hydrated[4]

HCP, health care professional.

References: 1. Johns Hopkins. *A Guide to Apheresis*. Baltimore, MD; Johns Hopkins Medicine. **2.** UC San Diego. *Plasmapheresis Patient Handout*. San Diego, CA: UC San Diego Health System. **3.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **4.** Ohio State University. Apheresis. https://healthsystem.osumc.edu/pteduc/docs/apheresi.pdf.

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Leukapheresis for CAR T Cell Therapy

- CAR T cell manufacturers use collection protocols that target the MNC layer, which contains mature T lymphocytes[1]
- Monocytes are selectively depleted to enrich for CD3+ T cells in the final leukapheresis product[1-3]
- Mobilization (ie, use of growth factors to stimulate cells out of bone marrow) is not required since these cells are already in the blood[2,3]

A single leukapheresis session of **2-5 hours is typically sufficient** to harvest the required number of cells for CAR T cell manufacturing[2,4]

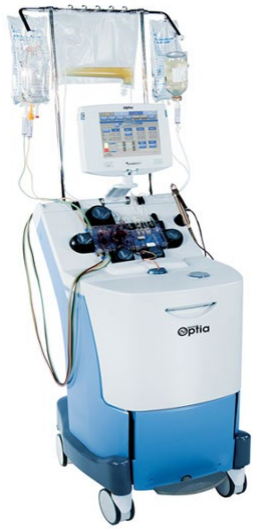
MNC, mononuclear cell.

References: 1. Juliano L, et al. *Cell Gene Ther Insights*. 2018;4:327-336. **2.** McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **3.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **4.** Korell F, et al. *Cells*. 2020;9:1225.

Leukapheresis Instrumentation

There can be wide variation in leukapheresis training, collection protocols, and collection equipment across clinical sites[1]

Spectra Optia®



Fenwal Amicus®

Two examples of FDA-cleared machines commonly used to collect leukapheresis product in accordance with CAR T cell protocols and standards are the **Spectra Optia®** and **Fenwal Amicus®**[2]

References: 1. Juliano L, et al. *Cell Gene Ther Insights*. 2018;4:327-336. **2.** Fesnak A, et al. *Transfus Med Rev*. 2016;30:139-145.

Technical and Quality Agreements for Leukapheresis

The product-specific protocols for collecting the leukapheresis product are aligned with the technical standards for CAR T cell production

- Pharmaceutical companies undergo a rigorous qualification and contracting process with apheresis facilities that can perform collections for its CAR T cell therapy products
- Additionally, on-site inspections may be performed
- Processes are defined for training personnel, tracking and verifying product identity, and many other aspects

Reference: Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141.

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Scheduling

Whether leukapheresis will be conducted internal or external to the CAR T cell therapy treatment center is decided by the treating center and depends on its in-house capabilities. Sufficient time is needed to perform[1,2]:

Close communication between the treating center, apheresis facility, and CAR T cell manufacturing facility is important throughout this process to deliver CAR T cell therapy to patients as safely and as quickly as possible[1]

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Preservation, Storage, and Shipping

Cell therapy products are extremely sensitive to temperature excursions[1]

- Cold preservation of the leukapheresis product is necessary immediately after collection[1]
- There are 2 types of cold preservation, which may be product-specific[1]
  - Short-term refrigerated storage (2° to 8°C), to slow down cellular metabolism and reduce physiologic stress that can damage or kill cells[1,2]
  - Long-term cryopreservation (-80° to <-150°C), to help preserve cells in a stable state[1,2]
- Once preserved, leukapheresis material is sent to the product manufacturer's central cell-processing facility in a validated shipping container that maintains product temperature[3]

References: 1. Juliano L, et al. *Cell Gene Ther Insights.* 2018;4:327-336. **2.** Rafiq QA, et al. *Cell Gene Ther Insights.* 2017;3:335-344. **3.** Better M, et al. *Cell Gene Ther Insights.* 2018;4:173-186.

Summary

Leukapheresis is a specific type of apheresis that refers to the collection of white blood cells from the peripheral blood[1]

Before undergoing leukapheresis, patients must meet certain criteria per institutional protocols[1-3]

CAR T cell manufacturers use collection protocols that target the MNC layer and, more specifically, non-mobilized CD3+ T cells within that class of cells[1,4,55]

Different machines and techniques may be employed to collect and ship leukapheresis products in accordance with the manufacturer's CAR T cell product-specific apheresis protocols and standards[3,4,6,7]

Close communication between the CAR T cell therapy treating center, apheresis facility, and CAR T cell manufacturing facility is important throughout the leukapheresis process[1]

MNC, mononuclear cell.

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Perica K, et al. *Biol Blood Marrow Transplant.* 2018;24:1135-1141. **3.** Fesnak A, et al. *Transfus Med Rev*. 2016;30:139-145. **4.** Juliano L, et al. *Cell Gene Ther Insights*. 2018;4:327-336. **5.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **6.** Rafiq QA, et al. *Cell Gene Ther Insights*. 2017;3:335-344. **7.** Better M, et al. *Cell Gene Ther Insights*. 2018;4:173-186.

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