Final Product Infusion Handbook for External Sites

Therapeutic Cell Production Core

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1. INTRODUCTION

1.1. TCPC Final Products are patient-derived, protocol-specific, expanded and cryopreserved T cell products. Single products typically are produced as a mixed culture of CD8-Enriched and CD4-Enriched T cells. Dual products typically are produced as two individual sub-products, one consisting of CD8-Enriched T cells and one consisting of CD4-Enriched T cells. Final products are suspended in CryoStor-CS5 (5% DMSO) and are generally contained within a CellSeal vial.

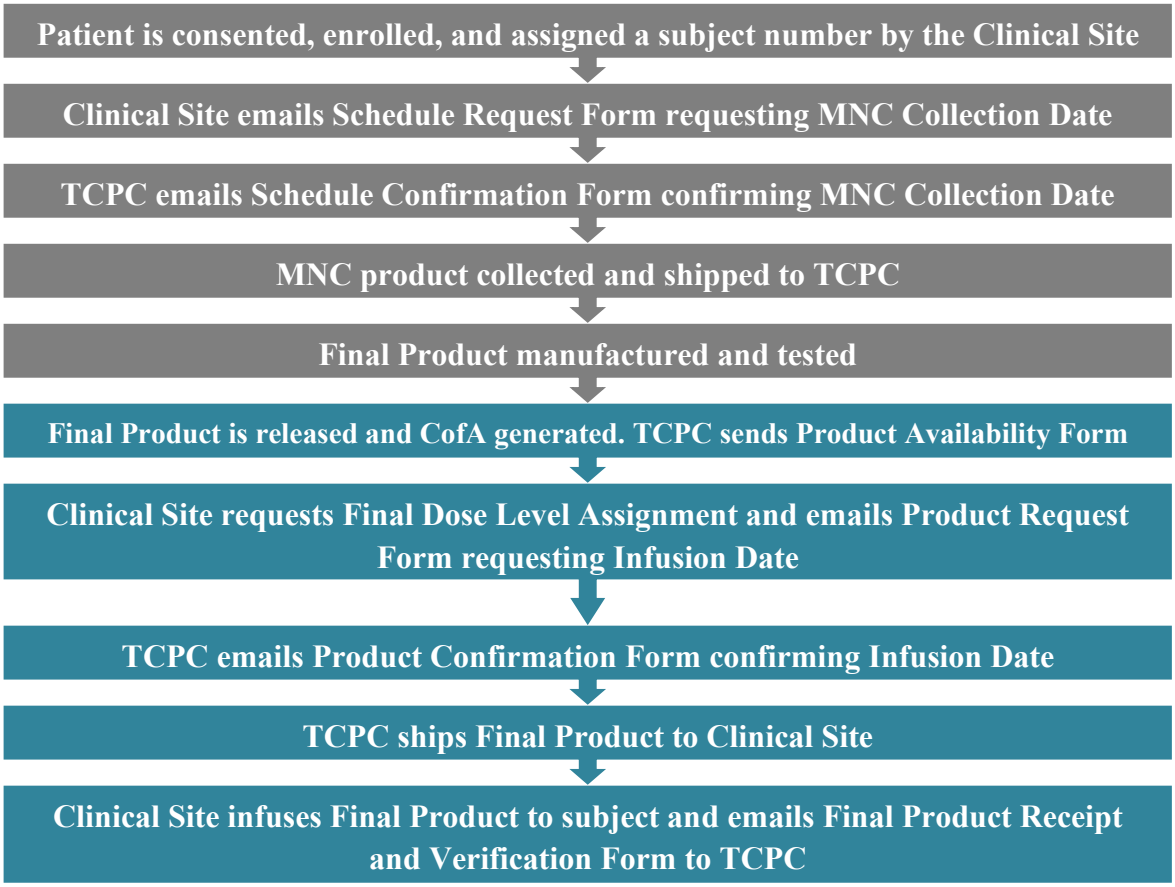
1.2. Products are shipped within a LN_2 dry-shipper via courier and vials are thawed prior to infusion to research subjects.

2. TRAINING

2.1. Prior to initiating a study at each Clinical Site, a member of the TCPC team will provide training to Clinical Site team members on receipt, handling, and infusion.

2.1.1. If training has previously been provided for another study with an equivalent infusion protocol, then additional training by TCPC is not required.

3. PROCESS OVERVIEW



4. PRODUCT REQUEST AND SHIPMENT TO CLINICAL SITE

4.1. Product Request for Infusion

4.1.1. When the product has been manufactured, released by Quality Assurance, and CofAs have been generated, TCPC will send the Clinical Site a ***Product Availability Form***.

4.1.1.1. If product fails release testing, study sponsor and study PI will be notified.

4.1.2. Based on product availability, the site staff should determine the patient's planned treatment schedule.

4.1.3. Once the infusion date has been established, the site staff will request product shipment by completing and sending the ***Product Request Form*** to TCPC which includes the Infusion date and location, current patient weight, and cell dose.

NOTE: The Clinical Site must obtain a Final Dose Level Assignment from Seattle Children's Therapeutics Clinical Trials Management (CTM) prior to submitting a Product Request Form to TCPC.

4.1.4. Product Request Forms should be sent to TCPC a minimum of 5 business days prior to the infusion date to ensure delivery accommodation Generally, within 1 business day, TCPC will send the Clinical Site a ***Product Confirmation Form*** which includes the confirmed cell dose and infusion date, as well as product delivery date.

4.1.4.1. Enclosed in the Dry Shipper containing the Final Product for infusion, TCPC will send the Clinical Site a copy of the protocol-specific "*Calculation of Infusion Volume"* Attachment from the *"Preparation for Infusion of Subject Cell Product"* document. This attachment includes the volume of product to infuse.

4.1.5. The subject may be re-treated with the remaining dose(s) if they meet the criteria for re-treatment. See study protocol for details.

4.1.5.1. If subject meets criteria for re-treatment and the re-treatment date has been established, the site staff will request product shipment by completing and sending a new ***Product Request Form*** to TCPC which includes the re-treatment date and location, current patient weight, and cell dose.

4.1.5.2. TCPC will send the Clinical Site a new ***Product Confirmation Form*** which includes the re-treatment date, product delivery date, and cell dose.

4.1.5.3. TCPC will send the Clinical Site a new a copy of the protocol-specific "*Calculation of Infusion Volume"* Attachment from the *"Preparation for Infusion of Subject Cell Product"* document, which will be enclosed in the Dry Shipper containing the Final Product for Infusion. This attachment includes the volume of product to infuse.

4.2. **Shipment to Clinical Site**

4.2.1. Based on the information provided on the ***Product Request Form***, TCPC will coordinate shipment and delivery of the Final Product to the Clinical Site in a LN_2 Dry Shipper.

4.2.2. The shipment will be scheduled to arrive prior to the time infusion.

4.2.3. The LN_2 Dry Shipper contains the following:

4.2.3.1. Temperature Data Logger

4.2.3.2. Box containing Final Product CellSeal cryovial(s)

4.2.3.3. Certificate of Analyses (CofA)

4.2.3.4. A copy of the Product Confirmation Form

4.2.3.5. A copy of the protocol-specific "Calculation of Infusion Volume" Attachment from the "Preparation for Infusion of Subject Cell Product" document

4.2.3.6. Final Product Syringe labels

4.2.3.7. Shipper Expiration Label (on exterior of shipper)

4.2.3.8. Courier Waybill/Shipper receipt documentation

4.2.3.9. Documentation for return of the shipper to courier and FedEx Ground® waybill

4.3. **Receipt of Shipper at the Clinical Site**

4.3.1. When the LN_2 Dry Shipper containing Final Product arrives at the site, the site staff receiving the shipper must sign the courier waybill to acknowledge receipt. **Do not open the shipping container until ready to thaw for infusion.**

4.3.2. Site staff receiving the Dry Shipper containing Final Product should perform the following activities:

4.3.2.1. Fill out the *Patient Information* section of the ***Final Product Receipt and Verification Form*** using the ***Product Request Form***.

4.3.2.2. Ensure the product lot number on the waybill matches the product lot number on the ***Final Product Receipt and Verification Form*** and document in *the Dry Shipper Receipt* section of the ***Final Product Receipt and Verification Form***.

4.3.2.3. Inspect shipping container for damage or leaks and document on ***Final Product Receipt and Verification Form***.

4.3.2.4. Verify the date and time the patient is scheduled for infusion (listed on Product Request Form) will occur **prior to the shipper expiration** (See expiration label affixed to the outside of the shipping container; label example below).

4.3.2.4.1. *At the time of infusion*, verification will be completed again and documented on the ***Final Product Receipt and Verification Form***.

NOTE: Expiration Date and Time is assigned by TCPC for 8 days from time of shipper preparation and is recorded in the time zone where the infusion will take place.

5. PRODUCT LABELING

5.1. CellSeal Cryovial Label

5.1.1. Labeled CellSeal cryovial label will include the following information:

5.1.1.1. Product name

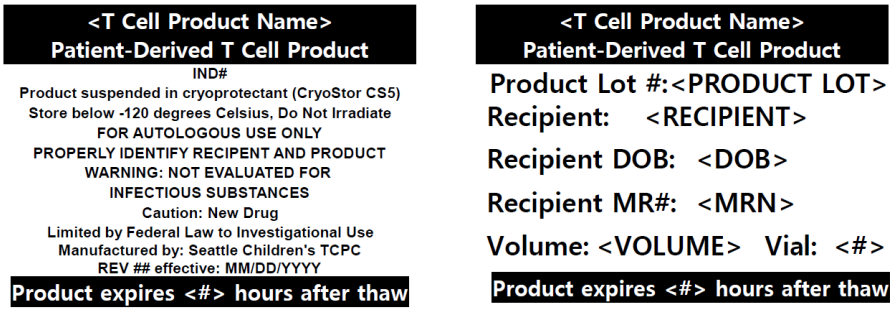
5.1.1.2. Study Subject ID/Lot Number

5.1.1.3. Subject Name

5.1.1.4. Subject Date of Birth

5.1.1.5. Subject MRN or Identifier

5.1.2. Example**:** ***CellSeal Cryovial label*** *(Flag-n-Vu, Two-sided butterfly labels)*



5.2. Product Syringe Labels

5.2.1. Product will be drawn up into a syringe for infusion. The syringe label will be sent clipped to the corresponding Certificate of Analysis from TCPC that accompany every product shipment. The site staff member preparing the syringe will complete the expiration information on the syringe label and affix the label to the syringe.

5.2.2. The syringe label will contain the following information:

5.2.2.1. Product name

5.2.2.2. Subject Name

5.2.2.3. Subject MRN or Identifier

5.2.2.4. Study Subject ID/Lot Number

5.2.2.5. Volume in Syringe

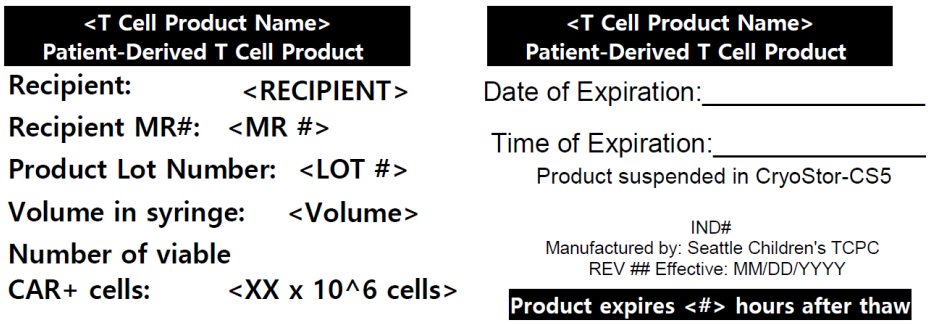
5.2.2.6. Number of Cells

5.2.2.7. A blank line to record the Date of Expiration

5.2.2.8. A blank line to record the Time of Expiration

5.2.2.9. Product expiration statement "Product expires four hours after thaw"

5.2.3. Examples: ***Syringe Labels*** (Flag-n-Vu, two-sided butterfly labels)



6. THAW AND PREPARATION FOR INFUSION

NOTE: Use of the CellSeal Automated Thawing System is preferred to thaw CellSeal vial(s) for infusion. If the CellSeal Automated Thawing System is not available, a waterbath set to 37°C ±3°C may be used instead.

6.1. Supplies and Equipment Needed

6.1.1. Assemble the following supplies prior to opening the Dry Shipper to retrieve the product:

6.1.1.1. For Single Final Products:

6.1.1.1.1. 1x syringe w/luer lock (1mL or 3mL, as needed)

6.1.1.1.2. 1x 18ga non-coring needle

6.1.1.1.3. 1x Luer Lock Plugs

6.1.1.2. For Dual Final Products:

6.1.1.2.1. 2x syringe w/luer lock (1mL or 3mL, as needed)

6.1.1.2.2. 2x 18ga non-coring needle

6.1.1.2.3. 2x Luer Lock Plugs

6.1.1.3. CellSeal Automated Thawing System

6.1.1.4. Alcohol Swabsticks

6.1.1.5. Povidone-iodine Swabsticks

6.1.1.6. Cryo-Gloves

6.1.1.7. Disposable absorbent barrier pad

6.1.1.8. Surgical scissors

6.1.1.9. Syringe Label (clipped to corresponding CofA)

6.1.1.10. ***Product Confirmation Form***

6.1.1.11. ***Final Product Receipt and Verification Form***

6.1.1.12. Additional supplies for waterbath thaws:

6.1.1.12.1. Waterbath

6.1.1.12.2. 2x IL bottle of sterile water

6.1.1.12.3. 70% Isopropanol spray bottle

6.1.1.12.4. Low-lint wipes

6.1.1.12.5. Thin plastic bag (i.e. Ziploc™ or equivalent)

6.2. Thaw Procedure

6.2.1. If performing a Dual Final Product infusion, the CD8-Enriched sub-product will be prepared and infused first, followed by the CD4-Enriched sub-product.

6.2.1.1. When the clinical team is ready to infuse the Final Product, verify the infusion date and time does not exceed the Dry Shipper Expiration Date and Time (recorded on the Dry Shipper Expiration Label located on the outside of the shipping container) and document in the *Product Inspection* section of ***Final Product Receipt and Verification Form***.

6.2.1.2. Open the Dry Shipper outer container and obtain the ***Product Confirmation Form***, the CofA(s), *Calculation of Infusion Volume* Attachment, and Final Product Syringe Labels from the document sleeve.

6.2.1.3. Verify that the information on the ***Product Confirmation Form*** matches the CofA (by read back with another staff member).

6.2.1.4. Verify the information listed on the ***Product Confirmation Form*** matches the information listed on the syringe label (by read back with another staff member).

6.2.1.5. Verify that the cell dose and infusion volume listed on *Calculation of Infusion Volume* Attachment matches the syringe label (by read back with another staff member).

6.2.1.6. For thawing CellSeal Vial(s) using the Autothawer:

6.2.1.6.1. Plug in the autothawer and select the desired profile (typically Rapid Thaw, 2mL vial, 1.5mL Fill Volume, -50°C Load Alarm, 10min Time Alarm). The indicator ring will turn yellow while the chamber is warming. When the device is at temperature, the indicator ring will turn green and the display will read "Ready to Load."

6.2.1.6.2. Proceed to step 6.2.3.

6.2.2. For thawing CellSeal Vial(s) using a waterbath:

6.2.2.1. Spray the interior of the water bath with 70% isopropanol and wipe with low-lint wipes.

6.2.2.2. Fill the water bath with approximately 2L of sterile water and heat to 37°C ±3°C.

6.2.3. Using aseptic technique, affix an 18ga non-coring needle to syringe luer port. Leave cap on needle.

NOTE: If multiple vials will be thawed, the dose will be drawn into a single syringe. A new needle will be placed on the syringe for each vial to be thawed.

6.2.4. For the first vial thaw only, place appropriate syringe label on the prepared syringe and set aside.

6.2.5. When ready to thaw, and either the Autothawer displays "Ready to Load" or the water bath is stable at 37°C ±3°C, open the shipping container and remove the chamber plug.

6.2.6. Pull on the Tyvek bag handles to pull out the bag containing samples. Remove the box containing the product and remove the vial from the box.

NOTE: Hold the vial by the tubing only. Refrain from touching the body of the vial as this can warm the outside of the vial and cause an alarm on the Autothawer.

6.2.7. If another vial or sub-product still remains in Tyvek bag, return the Tyvek bag to the Dry Shipper and insert the chamber plug to keep remaining sub-product chilled.

6.2.8. Record the thaw time in the *Product Inspection* section on the ***Final Product Receipt and Verification Form***.

6.2.9. Calculate the expiration time based on the thaw time, and record as the "Expiration Date and Time" on the syringe label affixed to the syringe and on the ***Final Product Receipt and Verification Form***.

6.2.9.1. Expiration Date and Time is calculated as **+2hrs** from the thaw for PLAT-02, ENCIT and Enlighten products.

6.2.9.2. Expiration Date and Time is calculated as **+4hrs** from the thaw for all other protocols.

NOTE: If multiple vials will be thawed, only the thaw time of the first vial will be recorded and used to assign the expiration date and time.

6.2.10. Verify the information on the cryovial label matches the information on the ***Product Confirmation Form*** (by read back with another staff member) and document on ***Final Product Receipt and Verification Form.***

NOTE: For all following steps in this process, ensure the cryovial remains upright and that no liquid (from inside or outside the vial) comes in contact with the filter inside the vial tubing.

6.2.11. For thawing vial(s) using the Autothawer perform step 6.2.13.

6.2.12. For thawing vial(s) using the waterbath, perform step 6.2.14.

6.2.13. Thawing vial(s) using the Autothawer:

6.2.13.1. Carefully unwrap the CellSeal Cryovial label from the vial and immediately secure to the tubing at the top of the vial. When attaching, ensure identifiers are visible and the filter line is visible. Ensure there is space to cut tubing above filter line.

6.2.13.2. Grasping the vial by the tubing, insert the vial into the chamber by pressing down until the ring turns purple and the chucks close around the vial.

NOTE: Removing the CellSeal Cryovial label can generate a "Vial Too Warm" alarm. This does not indicate a problem; select Continue by pressing Enter to proceed with thaw and make note of the error on the *Final Product Receipt and Verification Form*.

6.2.13.3. As the thaw begins, the indicator will glow blue and the progress bar will be displayed.

6.2.13.3.1. The ring will turn red if an error has occurred during the thaw process. Select "Continue" to continue thawing and make note of the error that occurred on the ***Final Product Receipt and Verification Form***.

6.2.13.4. When the thaw is complete, a tone will sound, the indicator ring will glow green, and the vial will be ejected from the chamber.

6.2.13.4.1. If an unsuccessful thaw occurred, the indicator ring will turn yellow and a different tone will sound. Record any error messages on the ***Final Product Receipt and Verification Form***. If error is related to anything other than "Vial to Warm" alarm, refer to site procedures and guidelines on reporting deviations.

6.2.13.4.2. If an additional vial will be thawed, press the ○ button on the Autothawer so the device can prepare for the next thaw. The indicator will glow orange, then green, when the device is at temperature.

6.2.13.4.3. Proceed to step 6.2.15.

6.2.14. Thawing vial(s) using the waterbath:

6.2.14.1. Place the vial in a thin plastic bag, immerse the bag into the waterbath, and agitate gently while thawing.

6.2.14.2. When vial has been mostly thawed with some ice slurry still present, remove vial from water bath and plastic bag, then spray a low-lint wipe with 70% IPA and gently wipe vial.

6.2.15. Inspect vial for damage or leaks and document on the **Product Receipt and Verification Form**.

6.2.15.1. If any are damage or leaks are seen, **do not proceed**. Contact TCPC immediately and refer to study site procedures and guidelines for deviation reporting.

6.2.16. Carefully remove protective seal from septum on bottom of cryovial.

6.2.17. Swab septum with iodine swabstick, then with alcohol swabstick and allow to air dry.

6.2.18. Using surgical scissors, carefully cut **tubing with filter** on top of vial **between** the seal and the filter. Ensure the filter remains within the tubing attached to the cryovial.

6.2.19. Remove cap from needle and carefully pierce septum of vial with needle.

6.2.20. Referring to a copy of the protocol-specific "*Calculation of Infusion Volume*" Attachment draw the required volume of cell suspension into the syringe.

6.2.21. Remove needle from septum and set shield on needle.

6.2.22. If drawing from multiple vials:

6.2.22.1. Using the same syringe and a new needle, repeat steps 6.2.3. to 6.2.21. to replace needle and thaw next vial until the syringe contains the required infusion volume.

6.2.23. Remove the needle from syringe and carefully cap syringe with female end of luer lock plug.

6.2.24. If applicable, transfer capped syringe containing Final Product to infusion location.

6.2.25. Confirm with bedside nurse that all patient information on syringe label matches the information on the patient's wrist band (by read back with another staff member). If any discrepancies are found, contact TCPC immediately.

6.2.26. If no discrepancies are found, transfer syringe containing Final Product to nurse for immediate infusion.

6.2.27. **IMPORTANT: Filters must not be used during the infusion of the product.**

6.2.28. **IMPORTANT: Do not irradiate the cells at any point.**

6.2.29. If performing a Dual Final Product infusion, repeat the Thaw Procedure for the second product (generally a CD4-Enriched fraction product).

6.2.29.1. **IMPORTANT: If there is an adverse reaction to the first product infused, do not proceed with second product infusion. Contact PI and TCPC for further details.** Refer to **Scheduling Playbook** for contact information.

6.2.30. Remove the label from each thawed and infused Final Product CellSeal vial and sticker in clinical subject study binder**.**

6.2.31. Destroy any uninfused product and unused labels, and document on ***Final Product Receipt and Verification Form***.

6.3. **Final Product Infusion Instructions**

6.3.1. Refer to Clinical Site SOP for infusion details

6.3.2. Dispose of biohazardous materials in accordance with the Clinical Site's biohazard disposal policy and the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.

NOTE: File all subject-related paperwork (i.e. TCPC Clinical Forms) within the clinical subject study binder or equivalent.

7. RETURNING THE SHIPPER

7.1. When the Final Product has been removed for infusion from the LN_2 Dry Shipper and the shipper is empty, it can be returned to the courier via FedEx Ground®.

NOTE: FedEx Ground® packages will not be picked by the FedEx Express® drivers as they are separate entities.

7.2. **Return Instructions**

7.2.1. Remove the enclosed "EMPTY" label from the document sleeve under flap "B" on the shipping container and sticker over the "Exempt Human Specimen" Label on the side of the shipping container.

If any label was used in this area for your shipment please place the enclosed "EMPTY" label over it.

7.2.2. Close flaps on the exterior of the Dry Shipper making sure that flap "B" is showing.

7.2.3. Remove the "STOP" insert from the shipping pouch to expose the Air Waybill for shipment to the courier.

Remove Stop Insert from inside shipping envelope on flap "B".
Throw away ONLY the Stop Insert.

7.2.4. Seal the top of shipping container with packing tape.

Seal top of white carton with packaging tape making sure to have flap "B" showing on the outside of the white carton.

7.2.5. Place Shipping continers in designated FedEx scheduled pickup location for return shipment to the courier. Refer to shipping label to verify FedEx shipment type (FedEx Ground® or FedEx Express®).

8. REVISION HISTORY

Revision	Effective Date	Summary of Changes
00	10/21/19	Initial version of document.
01	11/23/2020	Update product name. Update for single product infusion of the v2 product.
02	01/21/2021	Remove references to PLAT-06 from infusion handbook. Change document title and number to make non-protocol specific. Update to encompass both single and dual product infusions.
03	09/09/2022	Update materials for 18ga non-coring needle. Add more details for FedEx pickup instructions. Modify references for Preparation for Infusion Attachment. Update label templates. Changed Seattle Children's Research Institute to Seattle Children's Therapeutics.
04	12/08/2022	Add instructions for removing CellSeal label prior to insertion into CAT. Remove references to appendix. Add workflow for requesting a Final Dose Level Assignment from CTM.