4003: Cellular Therapy Product

This form must be completed for all products for recipients of non-HCT cellular therapy (including post-HCT DCI infusions). For recipients of hematopoietic cellular transplants (HCT), complete the Hematopoietic Stem Cell Transplant (HCT) Infusion (2006) form. For recipients of Donor Lymphocyte Infusions (DLI), complete the Donor Lymphocyte Infusion (2199) form.

The Cellular Therapy Product (4003) form is designed to capture product specific information for all products given to a recipient as part of a course of cellular therapy. A series of collections from the same donor that uses the same collection method, even if the collections are performed on different days, should be considered a single cellular therapy product if only one set of manufacturing steps are applied to the collected material.

If more than one type of cellular therapy product is infused as part of a single course of cellular therapy, each product type must be analyzed and reported on a separate Cellular Therapy Product (4003) form. A product from the same donor undergoing different manufacturing steps or manipulations is considered different products and require multiple Cellular Therapy Product (4003) forms if each product is infused separately.

However, if the cells underwent different manufacturing steps or manipulations and at the end of the manufacturing process were combined for a single infusion or administration, it will be considered a single product and it will require a single Cellular Therapy Product (4003) form.

For more information see Appendix D–How to Distinguish Infusion Types and Appendix E–Definition of a Product.

Links to sections of form:

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.
If you need to reference the historical Manual Change History for this form, please click here or reference the retired manual section on the Retired Forms Manuals.

Date	Manual Section	Add/ Remove/ Modify	Description

9/23/2022	4003: Cellular Therapy Product	Modify	Updated for new DLI reporting process: This form must be completed for all products for recipients of non-HCT cellular therapy (including post-HCT DCI ~~/ DLI"~~ infusions). For recipients of hematopoietic cellular transplants (HCT), complete the Hematopoietic Stem Cell Transplant (HCT) Infusion (2006) form. For recipients of Donor Lymphocyte Infusions (DLI), complete the Donor Lymphocyte Infusion (2199) form.
9/23/2022	4003: Cellular Therapy Product	Remove	Removed blue note box below question 1: ~~If your center considers this to be a Donor Lymphocyte Infusions (DLI), as reported on the Pre-CTED (4000) form, product name will not be auto-populated. Select **Other product** for the product name.~~
9/23/2022	4003: Cellular Therapy Product	Add	Added commercially available CAR-T product Carvykti™ to the blue note box below question 5: For commercially available products Kymriah®, Yescarta®, Tecaruts™, BreyanziTM, and Abecma®, and Carvykti™, report the tissue source as Peripheral blood.
9/23/2022	4003: Cellular Therapy Product	Add	Added commercially available CAR-T product Carvykti™to the blue note box below question 7: For commercially available products Kymriah®, Yescarta®, Tecaruts™, BreyanziTM, and Abecma®, and Carvykti™, report the cell type as Lymphocytes (unselected).
9/23/2022	4003: Cellular Therapy Product	Modify	Removed the reference to DLI: If the product (e.g., ~~DLI/~~ DCI) being infused as a cellular therapy is a portion from a prior HCT, the portion becomes the "entire" product for the purposes of this form. The product can then be further divided.
9/23/2022	4003: Cellular Therapy Product	Remove	Removed Example 3: ~~The recipient receives two DLI infusions and the notes do not specify additional infusions are to be given. Report '2' and submit the form. The recipient then goes on to receive another DLI infusion for the same indication using the same donor / product. The number reported here should be updated to trigger another Cellular Therapy Infusion (4006) form.~~
4/11/2022	4003: Cellular Therapy Product	Add	Instruction added for the preferred timepoint of viability when the product was cryopreserved: If the product was cryopreserved, viability post-thaw should be reported.
1/28/2022	4003: Cellular Therapy Product	Modify	Version 5 of the 4003: Cellular Therapy Product section of the Forms Instruction Manual released. Version 5 corresponds to revision 5 of the Form 4003.

Last modified: Sep 23, 2022

Q1-2: Cellular Therapy Product Identification

If more than one cell therapy product is infused, each product must be reported on a separate Cellular Therapy Product (4003) form. See the Cellular Therapy Essential Data Pre-infusion (4000) form, question 51 , for the definition of a product.

Question 1: Name of product:

The name of the product reported will be auto populated from what was reported on the Pre-Cellular Therapy Essential Data (4000) form. If the cellular therapy product infused is a commercially available or pre- commercial product, this question is used to disable questions related to manufacturing.

Question 2: Is the product out of specification? (only for commercially available products)

This question is answered for commercially available or pre-commercial products. According to the product label, indicate if the product met specification release criteria, they are also defined as nonconforming products. The FDA specifies a set of criteria that the manufacturers need to comply with in order to define a product as within the specifications. For example, the product viability might be below the specified FDA criterium, however the product is perfectly safe to be administered. In these situations, the manufacture will contact the treating physician and inquire whether the product should still be shipped to the institution. Patients are required to consent to infusion of a product out of specification. These infusions are done as part of an Expanded Access Protocol (EAP)-like format and in some rare instances as single patient Investigational New Product (IND).

This can be found in the patient records, or they will be enrolled into an out of specification protocol with a clinicaltrials.gov number (NCT ID). This NCT ID should be reported on the Cellular Therapy Essential Data Pre-infusion (4000) form.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
1	7/29/ 2021	Remove	Removed blue note box below question 1: ~~If your center considers this to be a Donor Lymphocyte Infusions (DLI), as reported on the Pre-CTED (4000) form, product name will not be auto-populated. Select **Other product** for the product name.~~	DLIs are no longer reported on the F4003.

Last modified: Sep 23, 2022

Q3-12: Cell Product Source

Question 3-4: Date of cell product collection

Report if the date of cell product collection is **Known** or **Unknown**. If the date of cell product collection is **Known**, report the date (YYYY-MM-DD) in question 4. If the date of cell product collection is **Unknown**, continue with question 5.

If the exact date is not known, refer to General Instructions, General Guidelines for Completing Forms for more information regarding reporting partial or unknown dates.

> ✻ Questions 5-8 allow for the selection of multiple tissue sources and cell types for a product. For example, if the product consists of two different types of lymphocytes, the source of cells will be peripheral blood and the cell types will be CD4+ and CD8+ lymphocytes. Also, in the case of a tumor vaccine, the sources will be tumor and peripheral blood and the cell type will be dendritic cells and tumor cell hybridomas.

Question 5-6: What is the tissue source of the cellular product? (check all that apply)

> ✻ For commercially available products Kymriah®, Yescarta®, Tecartus™, Breyanzi™, Abecma®, and Carvykti™, report the tissue source as **Peripheral blood**.

Select from the list the tissue source(s) of the cellular product being reported in this instance. If the source is selected as **Other tissue source**, specify the other source in question 6.

Tissue source of **lymph node** includes draining lymph node.

The tissue source for non-mobilized peripheral blood, peripheral blood apheresis, and MNCs should be reported as **peripheral blood**.

Continue with question 7.

Question 7-8: What is the cell type? (check all that apply)

> ✻ For commercially available products Kymriah®, Yescarta®, Tecartus™, Abecma®, and Carvykti™, report the cell type as **Lymphocytes (unselected)**.

Select from the list the cell type(s) of the cellular product reported in this instance. This should be the type of cell(s) harvested to make the product and / or in the product infused. Please note that “CAR-T” is not an option, CAR-T cells are manufactured from lymphocytes. If the cell type is selected as Other cell type,

specify the other cell type in question 8. All cell types selected here must also be reported on the Cellular Therapy Infusion (4006) form. Please refer to the Cellular Therapy Infusion (4006) section of the CIBMTR Forms Instruction Manual (questions 16-31) for descriptions of cell types.

Question 9-12: Where was the cellular therapy product manufactured / processed?

Questions 9-12 apply only when **Other *or *No product** name is reported in question 1. If a pre-commercial or commercially available product was selected in question one, continue to question 13.

If the product was manufactured by a pharmaceutical or biotech company, continue with question 11 and select **Pharmaceutical or biotech company** from the list. If the company is not in the dropdown list, select **Other pharmaceutical company** and report the name and location of the company in question 12.

If the product was manufactured by a **Cell processing laboratory off site** that is not a pharmaceutical / biotech company, continue with question 12 and report the name and location of the laboratory.

> ! If the product is from an NMDP donor used for a prior HCT, report that the product was manufactured by a “Cell processing laboratory at the same center as the product is being infused,” and continue with question 13.

If the product was manufactured by a **Cell processing laboratory at the same center as the product is being infused**, continue with question 13.

If the product was manufactured by another site not listed above, select **Other site**, specify the other site in question 10, and report the name and location where the cellular therapy product was manufactured / processed in question 12.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
5	7/29/ 2022	Add	Added commercially available CAR-T product Carvykti™ to the blue note box below question 5: For commercially available products Kymriah®, Yescarta®, Tecartus™, BreyanziTM, and Abecma®, and Carvykti™, report the tissue source as Peripheral blood.	Carvykti™ was approved for commercial infusion in Feb 2022.
7	7/29/ 2022	Add	Added commercially available CAR-T product Carvykti™ to the blue note box below question 7: For commercially available products Kymriah®, Yescarta®, Tecartus™, BreyanziTM, and Abecma®, and Carvykti™, report the cell	Carvykti™ was approved for commercial infusion in Feb

			type as Lymphocytes (unselected).	2022.

Last modified: Oct 14, 2024

Q13-15: Collection Procedure

This section applies to Autologous products only. If this was an allogeneic product, continue with the "Cell Product Manipulation" section.

Question 13-14: Specify the method of product collection:

Specify how the product was collected:

Bone marrow aspirate: a sample of liquid bone marrow is removed, usually from the hip bone, breastbone, or thigh bone.

Cord blood: a sample of blood from umbilical cord blood specimen. Cord blood is collected from the umbilical cord after a baby is born and is stored in a cord blood bank

Leukapheresis: removal of blood to collect specific white blood cells (e.g., lymphocytes, CD34+ stem cells, etc.).

Peripheral blood draw: a sample of blood is removed from veins by venipuncture

Tumor biopsy sample: sample taken from a biopsy

If the product was collected by a method not listed above, select **Other method** and specify the other product collection method in question 14.

Question 15: Number of collections

Report the number of collections it took to collect the necessary cells for the for the autologous product.

If a collection occurs, but results in insufficient volume or poor quality for product manufacturing, do not report the date or count it as part of the number of collections reported

Example 1. A collection is performed March 1st but has a suboptimal yield and is discarded. A second collection is performed March 4th resulting in a product that is used for infusion.

What to report: Report only **1 collection** (only the second collection will be reported)

Example 2. A collection is performed March 1st but has a suboptimal yield but has acceptable quality. A second collection is performed March 4th and the two are combined to use for a single product.

What to report: Report **2 collections** (both collections will be reported)

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)

.	.	.	.	.

Last modified: Jan 28, 2022

Q16-37: Cell Product Manipulation

This section applies only when **Other** or **No product** name is reported in question 1. If a pre-commercial or commercially available product was selected in question one, continue to question 38.

This section specifies any manipulation that was done to manufacture the final cellular therapy product.

Question 16: Were the cells in the infused product selected / modified / engineered prior to infusion?

Indicate **Yes** if the cells contained in the product were selected (i.e., selective retention of a population of desired cells through recognition of specified characteristics), modified or genetically engineered. Indicate **No** if the cells contained in the product were not selected, modified or genetically engineered in any way prior to infusion and continue with question 31.

Question 17: Specify the portion manipulated:

If the product (e.g., DCI) being infused as a cellular therapy is a portion from a prior HCT, the portion becomes the “entire” product for the purposes of this form. The product can then be further divided.

Indicate if the **Entire product** or a **Portion of the product** was manipulated. If the entire product was manipulated, continue with question 19.

Question 18: Was the unmanipulated portion of the product also infused?

Indicate **Yes** or **No** if the unmanipulated portion of the product was also infused.

Question 19: Was the same manipulation method used on the entire product / all portions of the product?

Indicate **Yes** or **No** if the same manipulation was used on the entire product or all portions of the product. All manipulations for each portion of the product should be reported in questions 20-37.

Question 20-21: Specify method(s) used to manipulate the product: (check all that apply)

Indicate the method(s) of manipulation.

Steps in Manipulation
If the manipulation consists of several steps, individual steps do not need to be reported as separate manipulations. For example, T-cell depletion that is part of expansion does not need to be reported.

Cryopreservation as a Manipulation
Do not report cryopreservation (including plasma removal as part of cryopreservation) as a method of manipulation

Cultured (ex-vivo expansion): cells were placed in culture to increase in number (i.e., to expand) allowing for sufficient cells for infusion. Continue with question 31.

Induced cell differentiation: cells were placed in culture to give rise to cellular elements with biological characteristics other than those of the cells being cultured (i.e., mesenchymal stromal cells cultured to make osteoblasts; pluripotent stem cells cultured to make neural cell precursors). Usually, the description of the process would include the term “differentiation of cells X into cells Y”. This scenario can be seen in regenerative medicine indications. Continue with question 31.

Cell selection – positive: the manipulation of a cellular therapy product that a specific cell population(s) is enriched. This may be achieved by using an antibody that binds to a specific population of cells (e.g., CD4+ selection). Continue with question 31.

Cell selection – negative: the manipulation of a cellular therapy product such that a specific cell population(s) is reduced. Continue with question 31.

Cell selection based on affinity to a specific antigen: the cellular product undergoes selection to isolate the target population based on the ability of the target population to bind or recognize a specific antigen (e.g., a T cell population recognizing viral proteins, or a protein associated with a cancer). Continue with question 31.

Genetic manipulation (gene transfer / transduction): cells are manipulated via gene transfer, a process by which copies of a gene are inserted into living cells to induce synthesis of the gene’s product; or transduction, a process by which foreign DNA is introduced into a cell by a virus or viral vector. These techniques deliberately alter the genetic material of an organism to make them capable of making new substances or performing new or different functions. Continue with question 22 to report the types of genetic manipulation.

Other cell manipulation: not fitting an above category. Specify the other cell manipulation in question 21 and continue with question 31.

Questions 22-37: These questions apply only if **Genetic manipulation** was selected in question 20.

Question 22-30: Specify the type(s) of genetic manipulations (check all that apply)

Viral transduction is a process by which nucleic acid (DNA) is introduced into a cell by a virus, followed by viral replication in the affected cell. Check the box for the virus(es) used in the viral transduction in question 22 and continue with question 31.

Lentivirus: Lentiviruses are members of the genus of retroviruses that have long incubation periods and cause chronic, progressive, usually fatal disease in humans and other animals.

Retrovirus: Retroviruses are any group of RNA viruses that insert a DNA copy of their genome into the host cell to replicate. HIV is an example of a Retrovirus.

Transposon: Transposons are discrete mobile sequences in the genome that can transport themselves directly from one part of the genome to another without the use of a vehicle such as phage or plasmid DNA. They move by making DNA copies of their RNA transcripts which are then incorporated into the genome at a new site.

Non-Viral transfection is the process of deliberately introducing naked or purified nucleic acids into eukaryotic cells. Check the box for the method(s) of non-viral transfection in question 22.

Electroporation: Electroporation is a process of introducing DNA or chromosomes into cells using a pulse of electricity to briefly open the pores in the cell membranes. Continue with question 31.

Other non-viral transfection: A different non-viral transfection method not previously listed was utilized. Specify the other non-viral transfection method in question 23 and continue with question 31.

Gene editing is a type of genetic engineering in which DNA is inserted or removed from a genome using artificially engineered nucleases. If gene editing is selected, specify which gene was edited in the manipulation in question 24. If an **'Other gene'** was edited, specify the other gene in question 25. Continue with question 31.

Non-native protein expression is a type of genetic engineering in which a gene is transferred codes for an antigen receptor other than one that may already be naturally present in the cell (e.g., T-cells have natural T-cell receptors [TCRs]; a transgenic TCR or a Chimeric Antigen Receptor [CAR] are non- native antigen receptors).

Chimeric Antigen Receptor (CAR): A cell-surface receptor that has been engineered to combine novel features and specificities from various sources to enhance its antigen specificity. Engineered T- cells or B-cells will produce the specialized receptor that will be capable of binding to an epitope on its target cell1.

The CAR construct consists of several genes that can exert different functions, such as augment the immune response by co-stimulation, increase affinity, and increase the time it persists in the circulation without being cleared. The CAR construct information is usually unique and may influence its effect against the disease or the severity of side effects. Specify which construct(s) was used in the making of the Chimeric Antigen Receptor (CAR) in question 26. If a construct was utilized that is not in the list, check **Other construct** and specify in question 27. Continue with question 31.

CD19bζ (zeta) is an antibody fused to CD3ζ (zeta) and should be reported as CD3ζ.

For more information related to the different constructs and their functions, see this article:

https://www.jci.org/articles/view/80010.

[1]NCIthesaurus: https://ncit.nci.nih.gov/ncitbrowser/

Suicide gene: Cells underwent manipulation to have cell suicide inducing transgenes inserted into the product. Specify the suicide gene in question 28. If **Other** is selected, specify the other suicide gene in question 29. Continue with question 31.

iCasp9 is inducible Caspase 9. CaspaCIDe® consists of an inducible caspase 9 (iCasp9) gene together with the small-molecule, bio-inert, chemical induction of dimerization (CID) drug, AP1903.

T-cell receptor: Heterodimeric antigen receptors present on the surface of T-cells. Continue with question 31.

Other genetic manipulation: Other genetic manipulation that does not fit into a category listed above. Specify the other genetic manipulation in question 30 and continue with question 31. An example of another genetic manipulation is EGFR (epidermal growth factor receptor).

Question 31: Was the product manipulated to recognize a specific target/antigen?

Indicate **Yes** if the cells were cultured or engineered so that the majority of cells in the end product are able to recognize or bind to a chosen target (e.g., proteins from a virus or a protein from a tumor). This manipulation can be done outside of the context of 'genetic manipulation'. If the product was not manipulated to recognize a specific target / antigen, select **No** and continue with question 38.

Question 32: Specify target: (check all that apply):

Specify if the target is **Viral**, **Tumor / cancer antigen**, or **Other target**.

If the target is **Viral**, select all target viral antigen(s) that apply to the product in question 33.

If the target is **Tumor / cancer antigen**, select all target tumor / cancer antigen(s) that apply to the product in question 35.

If the target is something other than viral or tumor/cancer antigen, select **Other target** and specify the other target in question 37.

Question 33-34: Specify the viral target(s): (check all that apply)

Select all target viral antigen(s) that apply to the product. If the target is **Other virus**, specify the virus in question
34.

Question 35-36: Specify the tumor / cancer antigen: (check all that apply)

Select all target tumor / cancer antigen(s) that apply to the product. If the target is **Other tumor / cancer**

antigen, specify the tumor / cancer antigen in question 36.

Question 37: Specify other target:

If the target is something other than viral or tumor / cancer antigen, specify the other target in question 37.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
17	7/29/ 2022	Modify	Removed the reference to DLI: If the product (e.g., ~~DLI/~~ DCI) being infused as a cellular therapy is a portion from a prior HCT, the portion becomes the “entire” product for the purposes of this form. The product can then be further divided.	DLIs are no longer reported on the F4003.

Last modified: Sep 23, 2022

Q38-46: Cell Product Analysis

This section applies only to products that are not commercially available. If a commercially available product (e.g., Kymriah® or Yescarta®, Tecartus™, Breyanzi™, Abecma®) or pre-commercial product was selected in question one, continue to question 47.

Question 38: Is the percentage of genetically modified cells known?

Answered for genetically engineered/manipulated cells only. The percentage of genetically modified cells, or transfection efficiency, is calculated as a percentage of transfected cells from all cells in the sample. There are a number of methods used to determine transfection efficiency including flow cytometry, fluorometry, microscopy, real-time quantitative PCR, etc.

This information will be available from the cell processing lab that is manufacturing the cellular product and may not be available in the medical record. Indicate **Yes** if transfection efficiency was done. If transfection efficiency was not done or it is not known if transfection efficiency was performed, select **No** or **Unknown**, respectively and continue with question 42.

Question 39: Date:

Specify the date (YYYY-MM-DD) when sample was taken for the transfection efficiency testing.

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 40: Percent of genetically modified cells:

Report the percent of genetically modified cells in the product. Round to the nearest whole number.

Question 41: Was the target percent of genetically modified cells achieved?

The target percent if genetically modified cells, or transfection efficiency target, will be defined by the protocol. Indicate **Yes** or **No** if the target defined by the protocol was met.

Question 42: Was viability of cells done?

Indicate if the viability of cells was done. If the product was cryopreserved, viability post-thaw should be reported.

If the viability of the cells was analyzed, select **Yes** and continue with question 43. If viability of the cells was not done or it is not known if completed, indicate **No** or **Unknown**, respectively and continue with question 47.

Question 43: Date:

Specify the date (YYYY-MM-DD) when the sample was analyzed to determine viability, not the date the results are available.

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 44: Viability of cells:

Report the percent viability. Round to the nearest whole number.

Question 45-46: Method of testing cell viability:

Indicate the method of testing viability.

7-AAD (7-aminoactinomycinD) and **Propidium iodide** are compounds that can stain dead cells but will not cross the membrane of living cells. Cytometric techniques are used to calculate the percentage of viable cells in a sample.

Trypan Blue is a technique where the dead cells become stained when in contact with the compound, but living cells remain impermeable to the dye. Cells are counted under a microscope to determine the percentage of viable cells in a sample.

If both methods of viability testing are performed, report 7-AAD results. If the cell viability was tested using a different method, select **Other method** and specify the method in question 46 and continue with question 47. If the method is not known, select **Unknown** and continue with question 47.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
42	4/11/ 2022	Add	Instruction added for the preferred timepoint of viability when the product was cryopreserved: If the product was cryopreserved, viability post-thaw should be reported.	Added for clarification

Last modified: Sep 23, 2022

Q47: Product Infusion

Question 47: Specify the total number of planned infusions of this product: (as part of the course of cellular therapy)

Report the number of infusions specified per protocol. This question is used to make the correct number of Cellular Therapy Infusion (4006) forms come due. Each infusion must be part of the protocol and will be given regardless of disease assessment.

✻ For infusions of Breyanzi™ (both commercially available and non-conforming products), which has both CD4+ and CD8+ components, report as a single infusion and complete a single Infusion Form 4006.

Example 1. The protocol specifies three infusions are to be given as part of the course of cellular therapy. Report the total number of planned infusions as “3”.

Example 2. The protocol specifies five infusions are to be given as part of the course of cellular therapy. The recipient will be assessed after the first three infusions to see if additional infusions will be tolerated (not based on disease status) and two more infusions may be given. Report the total number of planned infusions as “5”. If the last two infusions do not occur, submit a request to remove the forms via Center Support in the ServiceNow application.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
47	7/29/ 2022	Remove	Removed Example 3: ~~The recipient receives two DLI infusions and the notes do not specify additional infusions are to be given. Report ‘2’ and submit the form. The recipient then goes on to receive another DLI infusion for the same indication using the same donor / product. The number reported here should be updated to trigger another Cellular Therapy Infusion (4006) form.~~	DLIs are no longer reported on the F4003.

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