

# 4003: Cellular Therapy Product

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 appropriate HCT infusion form (Form 2006).

Form 4003 is designed to capture product specific information for all products/infusions 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, each product type must be analyzed and reported on a separate Form 4003. A product from the same donor undergoing different manufacturing steps or manipulations are considered different products and require multiple 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 Form 4003.

For more information see [Appendix D–How to Distinguish Infusion Types](#) and [Appendix E–Definition of a Product](#).

Links to sections of form:

[Q1: Cellular Therapy Product Identification](#)

[Q2-11: Cell Product Source](#)

[Q12-14: Collection Procedure](#)

[Q15-46: Cell Product Manipulation](#)

[Q47-55: Cell Product Analysis](#)

[Q56: Product Infusion](#)

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
1/24/2020	<a href="#">4003: Cellular Therapy Product</a>	Modify	Version 3 of the 4003: Cellular Therapy Product section of the Forms Instruction Manual released. Version 3 corresponds to revision 3 of the Form 4003.



# Q1: Cellular Therapy Product Identification

\* If more than one cell therapy product is infused, each product must be reported on a separate Form 4003.

## Question 1: Name of product:

The name of the product reported will be auto-populated from what was reported on Form 4000. This question is limited to commercialized products and is used to disable questions related to manufacturing. If the name of the product is not an option or if the product has no commercialized name (e.g. DCI/DLI product), select 'other product' from the list.

If a commercially available product is selected, several questions on this form will be disabled and cannot be answered.

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## Q2-11: Cell Product Source

### Question 2-3: Date of cell product collection

Report if the date of cell product collection is “known” or “unknown” for question 2. If the date of cell product collection is known, report the date (YYYY-MM-DD) in question 3. If the date of cell product collection is unknown, continue with question 4.

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 4-7 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/tumor cell hybridomas.

### Question 4-5: What is the tissue source of the cellular product? (check all that apply)

- \* For commercially available products Kymriah® and Yescarta®, 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 5 and continue with question 6.


### Question 6-7: What is the cell type? (check all that apply)

- \* For commercially available products Kymriah® and Yescarta®, report the cell type as “Lymphocytes (unselected)”.

Select from the list the cell type(s) of the cellular product being reported in this instance. This should be the type of cell(s) harvested to make the product and / or in the product infused. If the cell type is selected as ‘Other cell type’, specify the other cell type in question 7 and continue with question 8. All cell types selected here must also be reported on the Cellular Therapy Infusion Form 4006. Please refer to the 4006 Manual, Q18-46 for description of cell types.


If “cytotoxic T lymphocytes (CTLs)” is selected, a Form 2005 Confirmation of HLA Typing form will also need to be completed.

**Question 8-11: Where was the cellular therapy product manufactured / processed?**

 Questions 8-11 apply only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 12.

If the product was manufactured by a pharmaceutical or biotech company, continue with question 10 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 11. Continue with question 12.

If the product was manufactured by a **cell processing laboratory off site** that is not a pharmaceutical / biotech company, continue with question 11 and report the name and location of the laboratory. Continue with question 12.

 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 12.

If the product was manufactured by a **cell processing laboratory at the same center as the product is being infused**, continue with question 12.

If the product was manufactured by another site not listed above, continue with question 9 to specify the other site and report the name and location in question 11. Continue with question 12.

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# Q12-14: Collection Procedure

\* This section applies to Autologous products only. If this was an allogeneic product, continue to question 15.

## Question 12-13: 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.

**Leukapheresis:** removal of blood to collect specific white blood cells (e.g., lymphocytes, CD34+ stem cells, etc.) Continue with question 14.

**Byoptic sample:** sample taken from a biopsy, typically a tumor biopsy Other method: not fitting in a category listed above

If the product was collected by a method not listed above, select 'Other method' and specify the other product collection method in question 13. Continue with question 14.

## Question 14: Number of collections:

Report the number of days 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 the second collection

**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:* Both collections would be reported

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# Q15-46: Cell Product Manipulation

\* This section applies only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 47.

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

## Question 15: 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 and continue with question 16. 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 40.

## Question 16: Specify the portion manipulated:

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

Indicate the portion of the product that was manipulated. If the entire product was manipulated, select “entire product” and continue with question 18.

If a portion of the product was removed and manipulated, select “portion of product” and continue with question 17.

## Question 17: Was the unmanipulated portion of the product also infused?

Indicate “yes” if the unmanipulated portion of the product was also infused. Indicate “no” if the unmanipulated portion of the product was not infused.

## Question 18: Was the same manipulation method used on the entire product / all portions of the product?

If the same manipulation was used on the entire product or all portions of the product, indicate “yes”. If different manipulation methods were used indicate “no”. All manipulations for each portion of the product should be reported in questions 19-46.

## Question 19-20: 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 40.

**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 40.

**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 40.

**Cell selection – negative:** the manipulation of a cellular therapy product such that a specific cell population(s) is reduced. Continue with question 40.

**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 40.

**Genetic manipulation (gene transfer / transduction):** cells are manipulated via gene transfer, a process by which copies of a gene are inserted into living cells in order 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 in order to make them capable of making new substances or performing new or different functions. Continue with question 21 to report the types of genetic manipulation.

**Other cell manipulation:** not fitting an above category. Specify manipulation in question 20 and continue with question 40.



✿ Questions 21-39: Specify the type of genetic manipulation.

✿ This section only applies if “genetic manipulation” was selected in question 19.

### Question 21-29: Transfection:

Transfection is a process of deliberately introducing naked or purified nucleic acids by viral or non-viral methods into eukaryotic cells. If the product underwent transfection, continue with question 22. Else continue with question 30.

**Viral transduction:** 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. If “yes”, indicate the virus used in the viral transduction in questions 23 and 24. Indicate “no” if the product did not undergo viral transduction and continue with question 25.

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. Indicate “no” if a Lentivirus was not used for the viral transduction.

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. Indicate “no” if a Retrovirus was not used for the viral transduction.

**Non-Viral transfection:** Non-viral transfection is the process of deliberately introducing naked or purified nucleic acids into eukaryotic cells. If “yes”, indicate the method of non-viral transfection in question 26-29. Indicate “no” if the product did not undergo non-viral transfection and continue with question 30.

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 are able to move by making DNA copies of their RNA transcripts which are then incorporated into the genome at a new site. Indicate “no” if Transposons were not used for the non-viral transfection.

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. Indicate “no” if Electroporation was not used for the non-viral transfection.

Other non-viral transfection: Indicate “yes” if a different non-viral transfection method not previously listed was utilized. Specify the other non-viral transfection method in question 29.

**Question 30-32: Gene editing:**

Gene editing is a type of genetic engineering in which DNA is inserted or removed from a genome using artificially engineered nucleases. If “yes”, specify which gene was edited in the manipulation in question 31.

If “other gene” is answered for question 31, specify the gene in question 32. Indicate “no” for question 30 if the cells did not undergo gene editing.

**Question 33: Were cells engineered to express a non-native antigen receptor?**

Indicate “yes” if the cells underwent 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). Indicate “no” if the cells did not undergo transfer of such a gene and continue with question 38.

**Question 34-37: Specify the protein inserted into the cellular product:**

Specify which construct was utilized as part of the genetic manipulation process:

**T-cell receptor:** Heterodimeric antigen receptors present on the surface of T-cells. Continue with question 38.

**Chimeric Antigen Receptor (CAR):** A cell-surface receptor that has been engineered to combine novel features and specificities from various sources in order 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 cell<sup>1</sup>.

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 35. If a construct was utilized that is not in the list, check “other construct” and specify in question 36.

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

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

**Suicide gene:** Cells underwent manipulation to have cell suicide inducing transgenes inserted into the product. Specify the suicide gene in question 37.

**Question 38-39: Other genetic manipulation:**

Indicate “yes” for other genetic manipulation that does not fit into a category listed above and specify in question 39.

**Question 40: 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) and continue with question 41. This manipulation can be done outside of the context of ‘genetic manipulation’. If “no”, continue with question 47.

**Question 41: Specify viral target(s): (check all that apply):**

If the target is viral, continue with question 42.

If the target is tumor/cancer antigen, continue with question 44.

If the target is something other than viral or tumor/cancer antigen, continue with question 46.

**Question 42-43: Specify the target antigen: (check all that apply)**

Select all target viral antigen(s) that apply to the product. If the target is “other virus”, specify in question 43. Continue with question 47.

**Question 44-45: 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 in question 45. Continue with question 47.

**Question 46: Specify other target:**

If the target is something other than viral or tumor/cancer antigen as selected in question 41, specify the other target. Continue with question 47.

<sup>1</sup>NCIthesarus: <https://ncit.nci.nih.gov/ncitbrowser/>

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# Q47-55: Cell Product Analysis

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\* This section applies only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 56.

## Question 47: Was transfection efficiency done? (genetically engineered cells)

Answered for genetically engineered/manipulated cells only. 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. Indicate “yes” if transfection efficiency was done. Indicate “no” if transfection efficiency was not done and go to question 51. Indicate “Unknown” if it is unclear whether or not transfection efficiency was performed.

## Question 48: 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 49: Transfection efficiency:

Report the percent transfection efficiency. Round to the nearest whole number.

## Question 50: Was transfection efficiency target achieved?

Transfection efficiency target will be defined by the protocol. Indicate “yes” or “no” if the target defined by the protocol was met.

## Question 51: Was viability of cells done?

If the viability of the cells was quantified, select “yes” and continue with question 52. If viability of the cells was not done, indicate “no” or if it’s unclear if viability was done, indicate “Unknown” and continue with question 56.

## Question 52: Date:

Specify the date (YYYY-MM-DD) when the sample was collected to determine viability.

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 53: Viability of cells:**

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

**Question 54-55: Method of testing cell viability:**

Indicate the method of testing viability.

7-AAD (7-aminoactinomycinD) and Propidiumiodide 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 55.

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## Q56: Product Infusion

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### Question 56: 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 forms (Form 4006) come due. Each infusion must be part of the protocol and will be given regardless of disease assessment.

**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, please submit a request to remove the forms via Center Support in the ServiceNow application.

**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 Form 4006 Cellular Therapy Product form.

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