

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).

The 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. In addition to use in research, this information is used for quality assurance measures, both by the NMDP and the Cord Blood Banks.

A series of collections from the same donor that uses the same collection method and mobilization cycle, 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. Products from the same donor but obtained using different manufacturing steps are considered different products and require multiple 4003 forms, one for each product.

Additionally, if the cells were manipulated or modified by different methods and at the end of the manufacturing process are 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:

[Q1-18: Cellular Therapy Product Identification](#)

[Q19-20: Cell Product Source](#)

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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
4/ 20/ 18	4003: Cellular Therapy Product	Add	Added Cryopreservation as a Manipulation note box to the instructions for questions 31-32.
1/ 30/ 18	4003: Cellular Therapy Product	Add	Version 1 of the 4003: Cell Therapy Product section of the Forms Instruction Manual released. Version 1 corresponds to revision 1 of the Form 4003.

Q1-18: Cellular Therapy Product Identification

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

Question 1: Name of product:

The name of the product reported here must match what was reported on Form 4000 question 42. 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.

Question 2: Specify donor:

Indicate the donor type for this product. If the product is "off the shelf" or a "third party" donor product obtained from pharmaceutical companies or other corporate entities, donor type should still be identified.

An autologous product has cells collected from the recipient for his/her own use. Continue with question 4.

A related donor (allogeneic, related) is a blood-related relative. This includes syngeneic, monozygotic (identical) twins, non-monozygotic (dizygotic, fraternal, non-identical) twins, siblings, parents, aunts, uncles, children, cousins, half-siblings, etc. Do not include adoptive parents/children or stepparents/children. Continue with question 4.

An unrelated donor (allogeneic, unrelated) is a donor who shares no known ancestry with the recipient. Include adoptive parents/children or stepparents/children. Continue with question 3.

Question 3: Did NMDP/Be the Match facilitate the procurement, collection, or transportation of the product?

Distinguish if the product is an NMDP product or a non-NMDP product. Examples of non-NMDP donor registries include, but are not limited to: St. Louis Cord Blood Bank, Anthony Nolan, and StemCyte International Cord Blood Center. This information is included on the product label, the paperwork accompanying the product, and within the NMDP search/product documentation.

Question 4: Was the product a cord blood unit?

Indicate “yes” if the product was a cord blood unit.

- If the product was an **autologous** cord blood unit, continue with question 8 to report the non-NMDP CBU ID.
- If the product was a **related** cord blood unit, continue with question 8 to report the non-NMDP CBU ID.
- If the product was an **NMDP unrelated** cord blood unit, continue with question 5 to report the NMDP CBU ID.
- If the product was a **non-NMDP unrelated** cord blood unit, continue with question 8 to report the non-NMDP CBU ID.

Indicate “no” if the product was not a cord blood unit.

- If the **autologous** product was not a CBU, continue with question 19.
- If the product was **related** but not a CBU, continue with question 14 to report donor DOB.
- If the unrelated donor was **NMDP** but not a CBU, report the NMDP donor ID in question 6
- If the unrelated donor was **non-NMDP** but not a CBU, report the non-NMDP unrelated donor ID in question 7

Question 5: NMDP Cord Blood Unit:

Report the NMDP Cord Blood Unit ID. This information is included on the product label, the product insert accompanying the product, and within the NMDP search/product documentation. The ID is always numeric and begins with “9” (e.g., 9000-0000-0). If the product ID does not begin with a “9,” the product may not be an NMDP cord blood unit and the source of the product should be double-checked. Continue with question 19.

Question 6: NMDP Donor ID:

Report the NMDP Donor ID. This information is included on the product label, the product insert accompanying the product, and within the NMDP search/product documentation. The ID is always numeric (e.g., 0000-0000-0) and is unique for each donor, assigned by the NMDP. Continue with question 19.

Question 7: Non-NMDP unrelated donor ID: (not applicable for related donors)

Do not complete this field if the recipient has an NMDP donor, a related donor, or a cord blood donor. This ID is often located on the product label, the product insert accompanying the product, and the registry-specific search/product documentation. Continue with question 9.

Question 8: Non-NMDP cord blood unit ID: (include related and autologous CBUs)

Examples of non-NMDP donor registries include, but are not limited to: St. Louis Cord Blood Bank and StemCyte International Cord Blood Center. This ID is often located on the product label, the paperwork accompanying the product, and registry specific search/product documentation. Enter the non-NMDP cord blood ID. Note that some cord blood banks can ship their units either through the NMDP or directly to the center. Carefully review the accompanying documentation to determine which is appropriate for your unit. You may wish to consult with your center's Transplant Coordinator, as they will have insight as to how the product was acquired. Continue with question 9.

Question 9: Is there an ISBT DIN number associated with the product?

Report "yes" if there is an International Society of Blood Transfusion (ISBT) Donation Identification Number (DIN) associated with the product. If the product is a cord blood unit, continue with question 10, all other products continue with question 12. If the product has an ISBT label on it, the ISBT DIN number is in the upper left-hand corner and consists of a letter followed by 12 numbers, two numbers on the end, and a letter in a box. Example below:

W0000 00 123456 8 A

Please find additional information regarding the ISBT DIN numbers and traceability at [ISBT 128 Basics](#). For example, you may see a barcode with an alphanumeric string below it.

Report "no" if there isn't an ISBT DIN associated with the product. If the donor is auto, continue with question 19. If the donor is related continue with question 14. If the donor is unrelated, non-NMDP continue with question 12.

Question 10: Is the CBU ID also the ISBT DIN number?

Answered only for cord blood units. Report "yes" if the non-NMDP CBU ID is the same as the International Society of Blood Transfusion (ISBT) Donation Identification Number (DIN) and continue with question 12.

If the CBU ID is not the same as the ISBT DIN number, select "no" and continue with question 11.

Question 11: Specify the ISBT DIN number:

Report the ISBT DIN number using the letter, 12 digits, 2 numbers on end, and the letter in the box. See question 9 form an explanation on ISBT DIN.

Question 12-13: Registry or UCB Bank ID:

Specify the registry used to obtain the adult donor or umbilical cord blood unit. The [Bone Marrow Donors Worldwide](#) codes have been adopted to avoid submitting the entire name and address of the donor registry.

For example, the registry code for Belgium donors is (B) but Belgium cord blood units the registry code is (BCB).

Some common banks that do not list with BMDW have been added to the [Form 2006 revision 4](#) list, including St Louis Cord Blood Bank (SLCBB) and Viacord (VIAC).

If the donor was found through DKMS, report the registry that facilitated the cellular therapy product. Some registries may be listed more than once with BMDW (once for marrow/PBSC products and differently for cord blood products). Ensure that the appropriate code for the product was selected, because distribution of data is dependent on the code.

If there is no match code for the adult donor registry or cord blood bank, provide the registry's official name in the "Specify other registry" field.

Please ensure that the registry you are entering under "other" is not already listed in the pull-down list for question 12. Entries such as NMDP adult donors, NMDP cords, and New York Cord Bank each have their own entries above.

Question 14-15: Date of birth (donor / infant):

For related donors only, report if the donor's/infant's date of birth is "known" or "unknown" for question 14. If the donor's/infant's date of birth is known, report the date of birth (YYYY-MM-DD) in question 15. If the donor's/infant's date of birth is unknown, continue with question 16.

Question 16-17: Age (donor / infant):

For related donors only, if the DOB is unknown, report if the donor's/infant's age is "known" or "unknown" for question 16. If the donor's/infant's age is known, report the donor's/infant's age at the time of product collection in question 17. Report the age in months if the recipient is less than 1 year old, otherwise report the age in years. If the donor's/infant's age at collection is unknown, continue with question 18.

Question 18: Sex (donor / infant):

For related donors only, indicate the donor's biological sex as "male" or "female." For cord blood units, report the infant donor's sex.

Q19-20: Cell Product Source

Question 19-20: Date of cell product collection

Report if the date of cell product collection is “known” or “unknown” for question 19. If the date of cell product collection is known, report the date (YYYY-MM-DD) in question 20. If the date of cell product collection is unknown, continue with question 21.

If the exact date is not known, General Instructions, [General Guidelines for Completing Forms](#) for more information regarding reporting partial or unknown dates.

Q21-26: Collection Procedure

* This section applies to Autologous infusions only. If this was an allogeneic infusion, continue to question 27.

Question 21: Did the recipient have more than one mobilization event to acquire cells?

Stem cells do not typically circulate in the bloodstream. Therefore, in order to increase the quantity of cells for collection, an agent is frequently given to the autologous recipient. The purpose of the agent is to move the stem cells from the bone marrow into the peripheral blood. This practice is often referred to as mobilization or priming. Occasionally, a bone marrow product may be primed using a growth factor.

For the purposes of this manual, the CIBMTR defines a mobilization event as the planned administration of growth factors or systemic therapy designed to enhance stem cell collection. If the donor requires an additional mobilization at a later date to collect an additional product, this should be considered an additional mobilization event. If the mobilization methods change (e.g., plerixafor is added starting on Day 3 of collection) this would be considered an additional mobilization event.

Example 1: An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection. Since the collection and mobilization methods remained the same over the duration of the collection, this is considered one mobilization event.

Example 2: An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection, but the cell count was poor. GM-CSF was administered and the autologous recipient was re-collected. This is considered two mobilization events due to the change in mobilization drugs administered.

Example 3: An autologous recipient was mobilized with G-CSF and underwent a one-day PBSC collection, but the cell count was poor. The recipient then received plerixafor to enhance the mobilization. This is considered two mobilization events due to the change in mobilization drugs administered.

If more than one mobilization event occurred, report the number of events in question 22, else continue with question 23.

Question 22: Specify the total number of mobilization events performed for this cellular therapy: (regardless of the number of collections or which collections were used)

Report the total number of mobilization events performed for this cellular therapy. Include all mobilization events, even if a product from the mobilization event for this cellular therapy was not used during the infusion. See examples in question 21 for more details.

Question 23: Number of collections:

Report the number of collections that occurred after the mobilization event(s) reported in questions 21 and 22. It is possible to have more than one collection per mobilization or a failed mobilization with no collection.

Example 1: (from above) An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection. The mobilization methods remained the same but the number of collections reported will be two.

Example 2: (from above) An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection, but the cell count was poor. GM-CSF was administered and the autologous recipient underwent another collection. This is considered two mobilization events, but three collections.

Question 24-25: Specify the method of product collection:

Specify how the product was collected:

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

Leukapheresis: removal of blood to collect specific blood cells

Byoptic sample: sample taken from a biopsy, typically a tumor biopsy.

Other method: not fitting in a category listed above.

If the method of product collection is selected as 'Other method', specify the other product collection method in question 25 and continue with question 26.

Question 26: Specify agent(s) used in the mobilization events: (check all that apply)

Report if any of the following agents were used in the mobilization event(s) reported in questions 21-22.

G-CSF: granulocyte colony-stimulating factor, filgrastim, Neupogen®

GM-CSF: granulocyte macrophage colony-stimulating factor, sargramostim, Leukine®

Peglygated G-CSF: pegfilgrastim, Neulasta

Plerixafor: Mozobil

Other CXCR4 inhibitor: examples include POL6326 and AMD3465. Report experimental and other CXCR4 inhibitors used to mobilize the donor here.

Q27-58: Cell Product Manipulation

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

Question 27: 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 28. 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 52.

Question 28: Specify the portion manipulated:

If the product being infused as a cellular therapy (e.g. DLI/DCI) 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 the portion of the product that was manipulated. If the entire product was manipulated, select “entire product” and continue with question 30.

If a portion of the product was removed and manipulated, select “portion of product” and continue with question 29.

Question 29: 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 30: 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 of the manipulations for each portion of the product should be reported in questions 31-58.

Question 31-32: 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. However, if T-cell depletion and/or washing are done as standalone manipulations, they should 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 52.

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 52.

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., CD3+ selection). Continue with question 52.

Cell selection – negative: the manipulation of a cellular therapy product such that a specific cell population(s) is reduced. Continue with question 52.

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 52.

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 33 to report the types of genetic manipulation.

Other cell manipulation: not fitting an above category. Specify manipulation in question 32 and continue with question 52.



Questions 33-51: Specify the type of genetic manipulation.
This section only applies if “genetic manipulation” was selected in question 31

Question 33-41: Transfection:

Transfection is a process of deliberately introducing naked or purified nucleic acids by viral or non-viral methods into eukaryotic cells. Continue with question 34 if the product underwent transfection or continue with question 42 if it did not.

Viral transduction: Viral transduction occurs when there is gene transfer by infection of a cell with nucleic acid by a virus, followed by viral replication in the affected cell. If “yes”, indicate the virus used in the viral transduction in questions 35 and 36. Indicate “no” if the product did not undergo viral transduction and continue with question 37.

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 transfection.

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 transfection.

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 38-41. Indicate “no” if the product did not undergo non-viral transfection and continue with question 42.

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 41.

Question 42-44: 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 56.

If “other gene” is answered for question 43, specify the gene in question 44. Indicate “no” for question 42 if the cells did not undergo gene editing.

Question 45: 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 62.

Question 46-49: 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-cells¹. Continue with question 50.

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 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 47. If a construct was utilized that is not in the list, check “other construct” and specify in question 48.

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 49.

Question 50-51: Other genetic manipulation:

Indicate “yes” for other genetic manipulation that does not fit into a category listed above and specify in question 51.

Question 52-53: 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 specify the target in question 53. This manipulation can be done outside of the context of ‘genetic manipulation’. If “no”, continue with question 59.

If the target is viral, continue with question 54.

If the target is tumor/cancer antigen, continue with question 56.

If the target is something other than viral or tumor/cancer antigen, continue with question 58.

Question 54-55: Specify viral target(s): (check all that apply):

Select all viral target(s) that apply to the product. If the target is “other virus”, specify in question 55. Continue with question 59.

Question 56-57: Specify the target antigen:

Select all target antigen(s) that apply to the product. If the target is “other target antigen”, specify in question 57. Continue with question 59.

Question 58: Specify other target:

If the product was manipulated to recognize a specific target/antigen that does fit in a category above, specify the other target. Continue with question 59.

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

Q59-67: Cell Product Analysis

Question 59: Was transfection efficiency done? (genetically engineered cells)

Answered for genetically engineered 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.

Question 60: 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 61: Transfection efficiency:

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

Question 62: 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 63: Was viability of cells done?

If the viability of the cells was quantified, select “yes” and report the date the sample was collected to determine viability in question 64 and the percentage of viable cells in question 65. Methods of testing cell viability are listed in question 66.

Question 64: 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 65: Viability of cells:

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

Question 66-67: 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 67.

Q68: Product Infusion

Question 68: 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, contact your CIBMTR CRC.