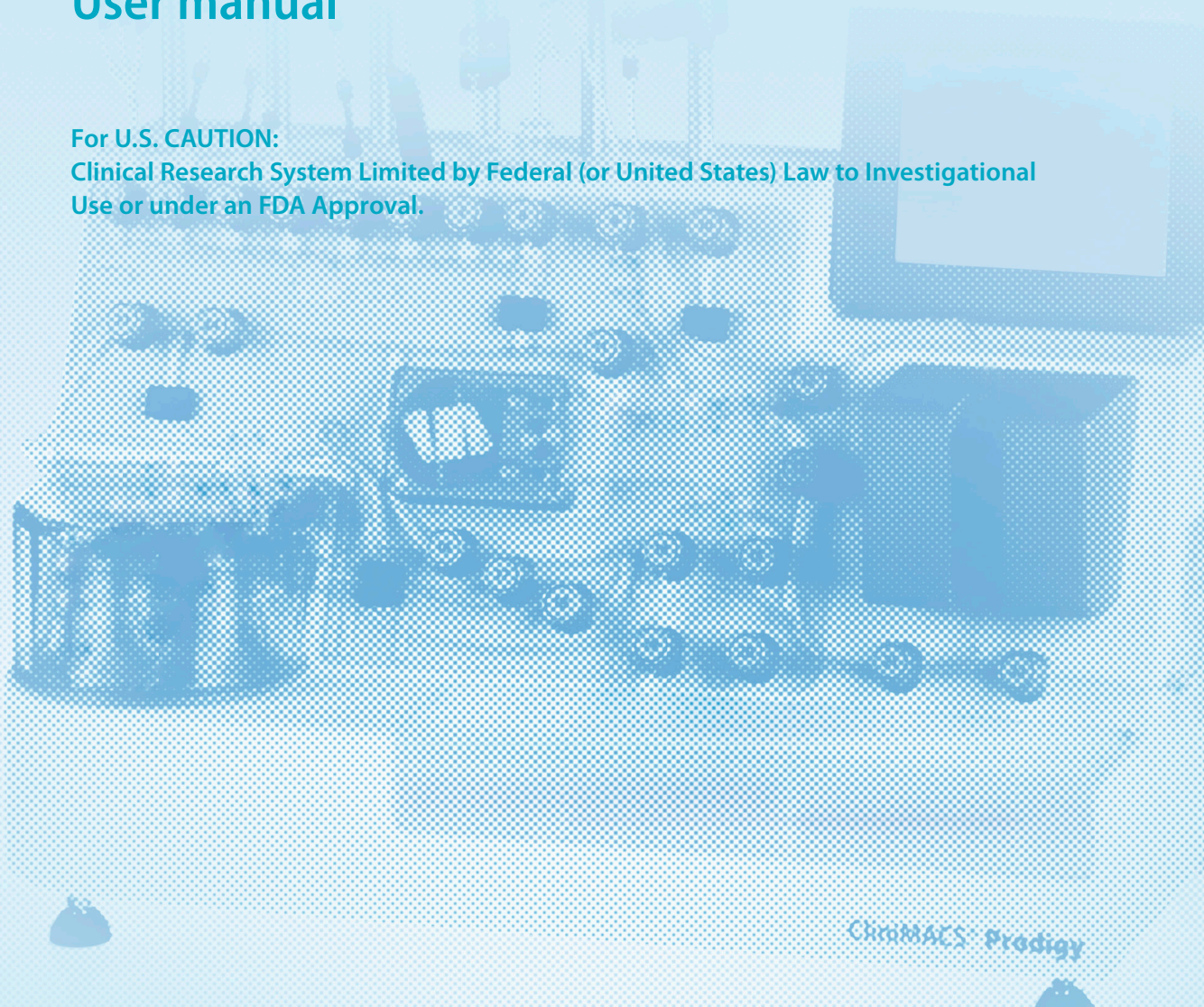
Miltenyi Biotec

CliniMACS Prodigy® LP-3-56 System

User manual

For U.S. CAUTION:
Clinical Research System Limited by Federal (or United States) Law to Investigational Use or under an FDA Approval.



The CliniMACS System components, including Reagents, Tubing Sets, Instruments, and PBS/EDTA Buffer, are designed, manufactured and tested under a quality system certified to ISO 13485. In the EU, the CliniMACS System components are available as CE-marked medical devices for their respective intended use, unless otherwise stated. In the US, the CliniMACS CD34 Reagent System, including the CliniMACS Plus Instrument, CliniMACS CD34 Reagent, CliniMACS Tubing Set TS and LS, and the CliniMACS PBS/EDTA Buffer, is FDA approved as a Humanitarian Use Device (HUD), authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this indication has not been demonstrated. Other products of the CliniMACS Product Line are available for use only under an approved Investigational New Drug (IND) application or Investigational Device Exemption (IDE) or FDA approval. CR/GMP products are for *ex vivo* cell processing only, and are not intended for human *in vivo* applications. For the manufacture and use of cellular products, national and international legislation and regulations must be followed.

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CliniMACS Prodigy® LP-3-56 System

User manual

Process version 2.x

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1

About this user manual

This user manual provides information for the use of the CliniMACS Prodigy LP-3-56 System. For further details on other processes running on the CliniMACS Prodigy, refer to the CliniMACS Prodigy user manual for the respective application. Instructions, warnings, precautions, and other important information for the use of the instrument as well as warnings and precautions concerning the handling of biohazardous materials and starting cell products are described in the CliniMACS Prodigy user manual (instrument). For instructions for use, e.g., warnings and precautions, concerning the CliniMACS Prodigy LP-3-56 System components, refer to the instructions for use provided for the respective component.

1.1 Essential information

⚠ WARNING

The operation of the CliniMACS Prodigy System must be performed by trained users only. Before putting the system into operation, carefully read, understand and retain the safety information, warnings, precautions, and instructions for proper operation of the CliniMACS Prodigy provided in the instructions for use of the CliniMACS Prodigy System components (including, without limitation, the safety information in the CliniMACS Prodigy user manual (instrument), chapter "Important safety information") and in any safety-related recommendations issued by Miltenyi Biotec. Pay special attention to all warnings shown on the instrument or provided with consumables and accessories. The user must adhere to all instructions and procedures at all times during the operation of the instrument, making sure that all safety information, warnings, precautions, and instructions are observed. Failure to follow the safety information, warnings, precautions, and instructions contained in the instructions for use can result in instrument malfunction, property damage, loss of target cells, personal injury, and/or death.

- Retain the instructions for use for future reference. They should be kept accessible and readily available together with all other safety and operating documentation during the entire life cycle of the instrument for all personnel responsible for installation, operation, and maintenance.

1.2 Presentational conventions

The following formatting styles are used to indicate specific information types in this user manual.

1.2.1 Text styles

• Bullet point list item with text	Indicates a list item
1. Numbered list item with text	Indicates a list item of a step-by-step instruction
A Capital letter list item with text	Indicates an optional list item
Bold <colored> text	Indicates software elements, for example, a button or a tab of the user interface
Bold ‹**black**› text	Indicates software elements, for example, a certain part of the user interface
See section 1.2.1 ´Text styles´	References to the section with the number 1.2.1 and the heading ´Text styles´
See Figure 2.1/Screen 2.1/Table 2.1	References to the first figure/screen/table in the second chapter.

1.2.2 Screens and figures

IMPORTANT

The screens and the figures in this manual are only representative screens and may differ slightly from those shown on the instrument.

1.2.3 Warning messages

The color and signal word of a warning message depend on the hazard level (see chapter 5 ´Warnings and precautions´). The following examples show the layout of warning messages at the beginning of a chapter/section where a hazard can occur.

⚠ WARNING

Type and source of hazard. Consequences of non-compliance.

- Measures to avoid the hazard.

⚠ CAUTION

Type and source of hazard. Consequences of non-compliance.

- Measures to avoid the hazard.

NOTICE

Type and source of hazard. Consequences of non-compliance.

- Measures to avoid the hazard.

The following example shows the layout of warning messages before an instructional step.

WARNING! Type and source of hazard. Consequences of non-compliance. Measures to avoid the hazard. Instructional text.

2
Glossary

2.1 Glossary of symbols and terms

An overview of symbols and terms used for the CliniMACS Prodigy System is provided in the CliniMACS Prodigy user manual (instrument). The glossary of symbols depicts the symbols used for labeling of the CliniMACS® Products.

3 Introduction

3.1 General information

The CliniMACS Prodigy LP-3-56 System includes the CliniMACS Prodigy, the CliniMACS CD3 Reagent, the CliniMACS CD56 Reagent, the CliniMACS Prodigy TS 320, and the CliniMACS PBS/EDTA Buffer. The recommended starting material is unmobilized leukapheresis product.

For the depletion of CD3-positive T cells, the CliniMACS Prodigy LP-3-56 System starts from unmobilized leukapheresis products. In the first separation step, the starting cell product is incubated with the CliniMACS CD3 Reagent. Subsequently, the magnetically labeled cells are depleted in a continuous separation process.

For the enrichment of CD56-positive cells, the LP-3-56 System starts from the CD3-depleted non-target intermediate. In the second separation step, the previous CD3-depleted material is incubated with the CliniMACS CD56 Reagent. Subsequently, the magnetically labeled cells are enriched in a continuous separation process. At the end of the process, the final cell product, which is depleted of CD3-positive cells and enriched of CD56-positive cells (depending on use case), is obtained for further applications.

The LP-3-56 Separation process includes three use cases:

1. CD3 depletion and CD56 enrichment
2. CD3 depletion (process buffer)
3. CD3 depletion (formulation solution)

3.2 Process

The separation procedure of CD3-negative and CD56-positive cells with the CliniMACS Prodigy LP-3-56 System is automated and requires only minimal preparation steps.

Install the CliniMACS Prodigy TS 320 on the instrument. Connect the CliniMACS PBS/EDTA Buffer, supplemented with human serum albumin (HSA), and the formulation solution or the rinsing solution to the tubing set, depending on the selected use case. Enter information on the starting cell product after priming of the tubing set. Based on the calculation of the cell counts, the CliniMACS Prodigy LP-3-56 System selects the appropriate stage number for the separations. Afterwards, the CliniMACS Reagents are connected to the tubing set and the starting cell product is transferred to the Application Bag.

Once the process has been started, all subsequent steps of the separation process are automated. Samples for quality control can be taken at the beginning and at the end of the process. The final cell product is then ready for clinical application or further processing (defined by the user of the system, e.g., culture, enrichment, or functional testing).

In order to allow a flexible separation strategy, several options (named use cases) are available to the user (see Figure 3.1). One of three use cases has to be chosen at the beginning of a manufacturing run:

Use case 1: CD3 depletion and CD56 enrichment
This option is chosen to run the complete process, including CD3 depletion, rinsing of the tubing set with rinsing solution and CD56 enrichment. The target cells (CD3-negative and CD56-positive cells) are eluted in formulation solution, ready for further applications.

Use case 2: CD3 depletion (process buffer)
This option is chosen when only the CD3 depletion from leukapheresis has to be performed. The target cells (CD3-negative cells) are eluted in process buffer, ready for further applications.

Use case 3: CD3 depletion (formulation solution)
This option is chosen when only the CD3 depletion from leukapheresis has to be performed. The target cells (CD3-negative cells) are eluted in formulation solution, ready for further applications.

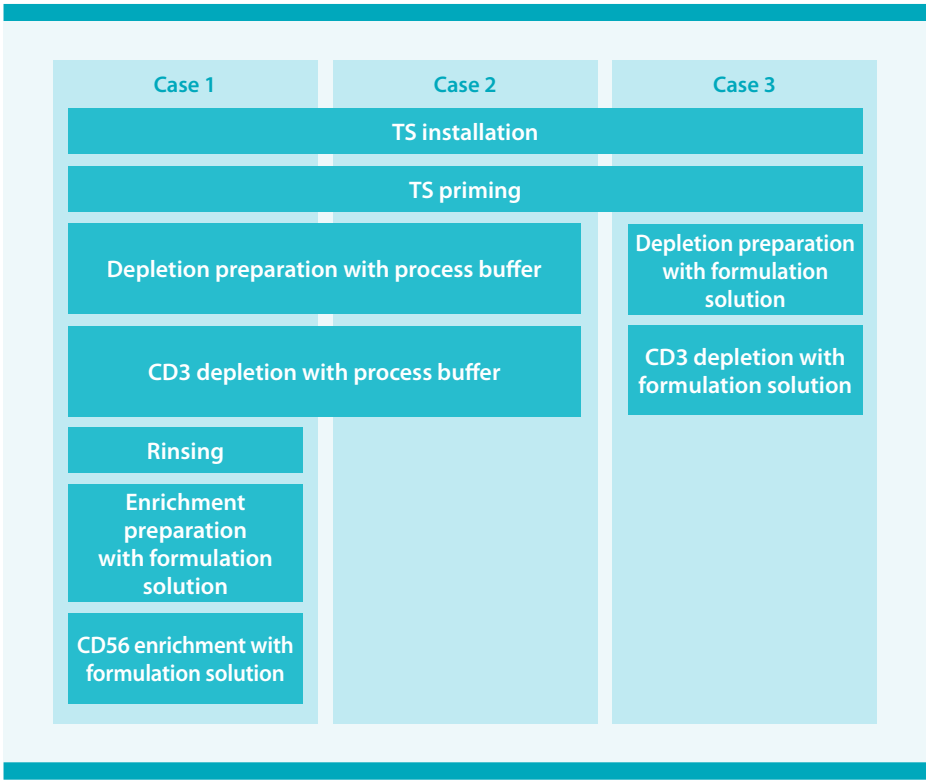


Figure 3.1: Versatility of the CliniMACS Prodigy LP-3-56 System

IMPORTANT

The process capacity is up to 9.6×10^9 of CD3-positive cells and up to 4.5×10^9 of CD56-positive cells from a total of 40×10^9 white blood cells (WBC). The sample volume specifications are 50–600 mL. The LP-3-56 Separation process must be used.

4

Materials required

The following section outlines the materials and consumables required for use with the CliniMACS Prodigy LP-3-56 System.

4.1 CliniMACS Prodigy LP-3-56 System components

The following CliniMACS Materials (see Table 4.1) are required for the depletion of CD3-expressing cells with or without enrichment of CD56-expressing cells:

CliniMACS Materials	Quantity Use case 1	Quantity Use case 2 and 3
CliniMACS Prodigy including accessories	1	1
CliniMACS CD3 Reagent	1 vial	1 vial
CliniMACS CD56 Reagent	1 vial	-
CliniMACS Prodigy TS 320	1 set	1 set
CliniMACS PBS/EDTA Buffer	9 L	6 L

Table 4.1: CliniMACS Materials required for the CliniMACS Prodigy LP-3-56 System

Only CliniMACS Products mentioned above have to be used in the LP-3-56 Separation process.

4.2 Additional materials

In addition to the CliniMACS Prodigy LP-3-56 System components, further materials and equipment are required for the CliniMACS Prodigy LP-3-56 System (see Table 4.2).

Materials	Comments
Biological materials	
Leukapheresis product	• Not older than 24 hours • <40.0 × 10^9 white blood cells with volume between 50 mL and 600 mL • Frequency of granulocytes below 10%
Human serum albumin (HSA)	To be added to the CliniMACS PBS/EDTA Buffer and to the formulation solution to a final concentration of 0.5% (w/v)
5% IgG solution	10 mL
Formulation solution	e.g., NaCl + 0.5% HSA Use case 1: 1 000 mL Use case 2: not required Use case 3: 2 000 mL
Rinsing solution	Use case 1: 1 000 mL aqua bidest for injection use Use case 2/3: not required
Consumables	
Syringes	10 mL, 50 mL (several)
Plasma transfer set	Depends on the chosen use case
3-Way Tube Adapter	Optional for connection of process solutions
Equipment	
Uninterruptable power supply unit	
Sterile docking device	
Cell counter	

Table 4.2: Additional materials required for the CliniMACS Prodigy LP-3-56 System

IMPORTANT

This protocol requires the use of components and materials which are not part of the CliniMACS Prodigy LP-3-56 System (e.g., human serum albumin [HSA]). Therefore, either components, which are registered as drugs in the country of the user, should be used or, if not available as registered drugs, all risks arising from these components should be evaluated by the user before application of the target cell product to humans. Special attention should be given to the stability of the target cell product in the chosen formulation solution.

5
Warnings and precautions

5.1 Hazard levels

The color and signal word of a warning message depend on the hazard level. The hazard level classifies the hazard, as described below.

⚠ WARNING

or WARNING! indicates a hazardous situation that, if not avoided, could result in death or serious injury.

⚠ CAUTION

or CAUTION! indicates a hazardous situation that, if not avoided, could result in minor or moderate injury.

NOTICE

or NOTICE: indicates information considered important, but not related to personal injury (e.g., messages relating to property damage).

The following example shows the layout of warning messages before an instructional step.

WARNING! Type and source of hazard. Consequences of non-compliance. Measures to avoid the hazard. Instructional text.

At all times, local working area safety instructions, policies, standards regarding good manufacturing practice, health, safety, and prevention of accidents must be adhered to.

Instructions, warnings, precautions, and other important information for the use of the CliniMACS Prodigy as well as warnings and precautions concerning the handling of biohazardous materials and starting cell product are described in the CliniMACS Prodigy user manual (instrument). For instructions for use, e.g., warnings and precautions, concerning the CliniMACS Prodigy LP-3-56 System components, refer to the instructions for use provided for the respective component.

6

Preparative steps

The depletion of CD3-expressing cells and enrichment of CD56-expressing cells with the CliniMACS Prodigy LP-3-56 System is automated and requires only a few preparative steps.

⚠ WARNING

Risk of infection. Preparative steps that are not performed in a sterile environment carry the risk of infection.

- Perform all preparative steps in a sterile environment (e.g., laminar flow hood) using aseptic techniques.

6.1 Testing of the starting cell product

⚠ WARNING

Risk of infection. Depending on the biological material used, contact may lead to severe personal injury or death.

- Always wear personal safety equipment in accordance with warnings and precautions, in particular if biohazardous material is or has been used.

Depending on the selected use case, the starting cell product used for the LP-3-56 Separation process needs to be tested for the following sample parameters:

- White blood cell (WBC) concentration ($\times 10^6$/mL), all use cases
- Frequency of CD3-positive cells (%), all use cases
- Frequency of CD3-negative and CD56-positive cells (%), use case 1
- Volume of starting cell product (mL), all use cases

The results obtained must be entered in the software during the set-up of the process.

To test the starting cell product, a fluorochrome staining for CD45, CD3, and CD56 is recommended. The percentage of all CD3-positive cells is used for parameter input related to the CD3 depletion part. The percentage of CD56-positive and CD3-negative cells is used for parameter input related to the CD56 enrichment part.
Contact Miltenyi Biotec Technical Support for analysis support, if required.

A dead cell exclusion must not be performed. All CD3-positive, CD56-positive and CD3-negative cells are included irrespective of non-specific binding of antibodies. Based on the cell parameter input, total WBC and labeled cell numbers are automatically calculated and the number of required loading stages for the separations is defined.

6.2 Preparation of process buffer

⚠ WARNING

Risk of infection. Depending on the biological material used, contact may lead to severe personal injury or death.

- Always wear personal safety equipment in accordance with warnings and precautions, in particular if biohazardous material is or has been used.

Supplement the required volume (refer to Table 4.1) of CliniMACS PBS/EDTA Buffer with HSA to a final concentration of 0.5% (w/v), i.e., add 20 mL of 25% HSA per liter of buffer. Use a plasma transfer set to connect the process buffer bags to each other. Ensure that the clamp on the transfer set is closed before connecting the buffer bags to each other. The supplemented buffer is henceforth referred to as "process buffer".

IMPORTANT
HSA is not a component of this system. Use only pharmaceutical-grade HSA approved in your country. Carefully read the package insert of the HSA used, particularly the section regarding hypersensitivity reactions and the risk of infection associated with HSA as a blood-derived product. The user must evaluate all risks arising from this material.

6.3 Preparation of formulation solution

Supplement the required volume (refer to Table 4.2) of a suitable formulation solution (e.g., NaCl) to a final concentration of 0.5% (w/v), i.e., add 20 mL of 25% HSA per liter of formulation buffer. The supplemented solution is henceforth referred to as "formulation solution".

If the formulation solution container is not suitable for connection to the CliniMACS Prodigy TS 320, transfer the formulation solution volume required into a suitable transfer bag prior to connection.

If more than one bag of formulation solution is required, use a plasma transfer set with an appropriate adapter, e.g., 3-Way Tube Adapter, to connect the bags to each other. Ensure that the fluid lines are closed, e.g. by clamping before connection of the bags.

6.4 Preparation of rinsing solution

Prepare the required volume (refer to Table 4.2) of aqua bidest for injection. This solution is henceforth referred to as "rinsing solution".

If the rinsing solution container is not suitable for connection to the CliniMACS Prodigy TS 320, transfer the required rinsing solution into a suitable transfer bag prior to connection.

6.5 Preparation of IgG solution

For this application, 10 mL of 5% IgG solution is required. If only higher concentrated IgG solution is available, IgG has to be diluted to a 5% (w/v) IgG solution, e.g., with CliniMACS PBS/EDTA Buffer.

IMPORTANT
IgG is not a component of the LP-3-56 System. Use only pharmaceutical-grade human IgG approved in your country. Carefully read the package insert of the human IgG used, particularly the section regarding hypersensitivity reactions and the risk of infection associated with human IgG as a blood-derived product. All risks arising from these materials must be evaluated by the user.

7

Separation process

7.1 Initialization of the CliniMACS Prodigy

Switch on the CliniMACS Prodigy with the power switch located on the rear side of the instrument.

Note: A user interface showing screens with instructions and images will guide through the entire procedure. Parts of the text shown in the screenshots in this user manual may slightly differ from the screens shown on the instrument. Use the touchscreen functionality and buttons on the menu and tool bar to operate the CliniMACS Prodigy. For details, refer to the CliniMACS Prodigy user manual (instrument).

⚠ CAUTION

Risk of process failure. If the incorrect drive shaft is installed on the instrument, the application process is not executed. The application process is designed for the use with the CliniMACS Prodigy TS 320 only. The CliniMACS Prodigy TS 320 contains a large CentriCult™ Chamber requiring a specific drive shaft. Ensure the drive shaft is installed by Miltenyi Biotec Instrument Service before using the tubing set.

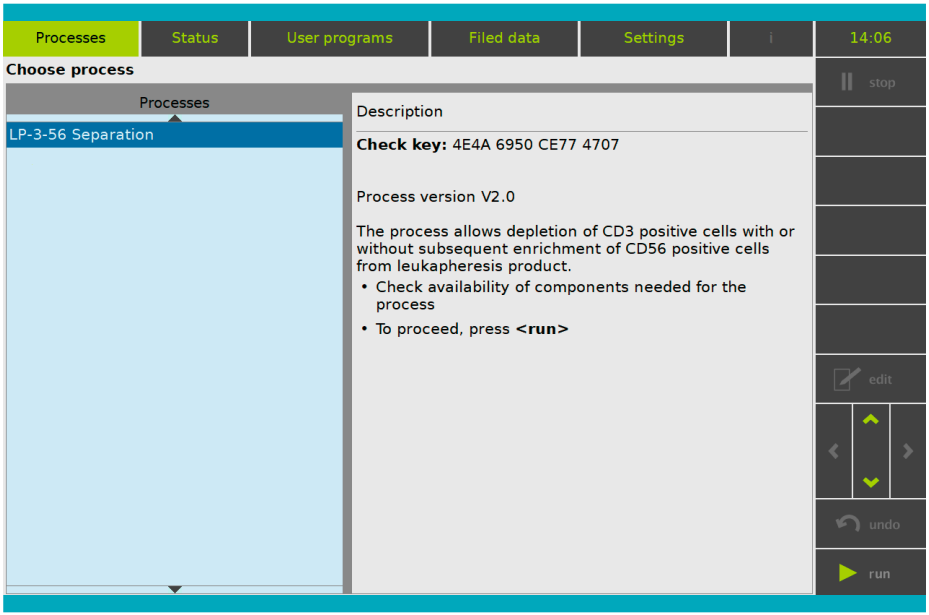
- Any CliniMACS Prodigy with SN 490 or lower needs the installation of the new drive shaft. Instruments with serial numbers higher than 490 are already equipped with the new drive shaft.
- Contact Miltenyi Biotec Technical Support if a drive shaft exchange is required.

⚠ CAUTION

Risk of process failure. If alarm signals are not recognized and the required actions are not executed or confirmed, there is the risk of process failure.

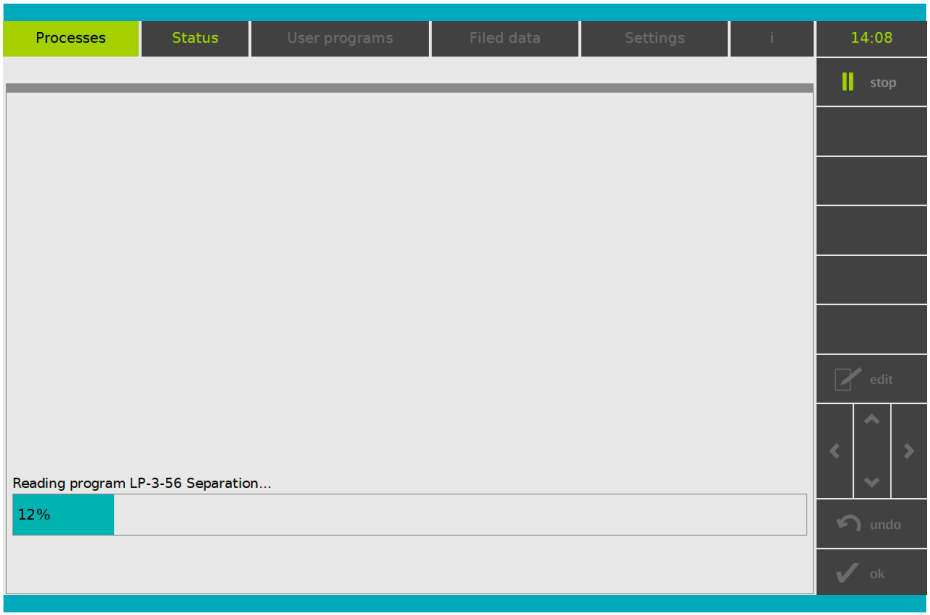
- Ensure that the user recognizes optical and acoustical alarm signals at any time during the process.

After the instrument initialization phase, the main screen is shown. Select the LP-3-56 Separation process and tap <run> to confirm the selection.



Screen 7.1: Choose separation LP-3-56 Separation process

The instrument performs a short self-test, shown on Screen 7.2 and indicates the remaining time on the process bar before the next screen is shown.

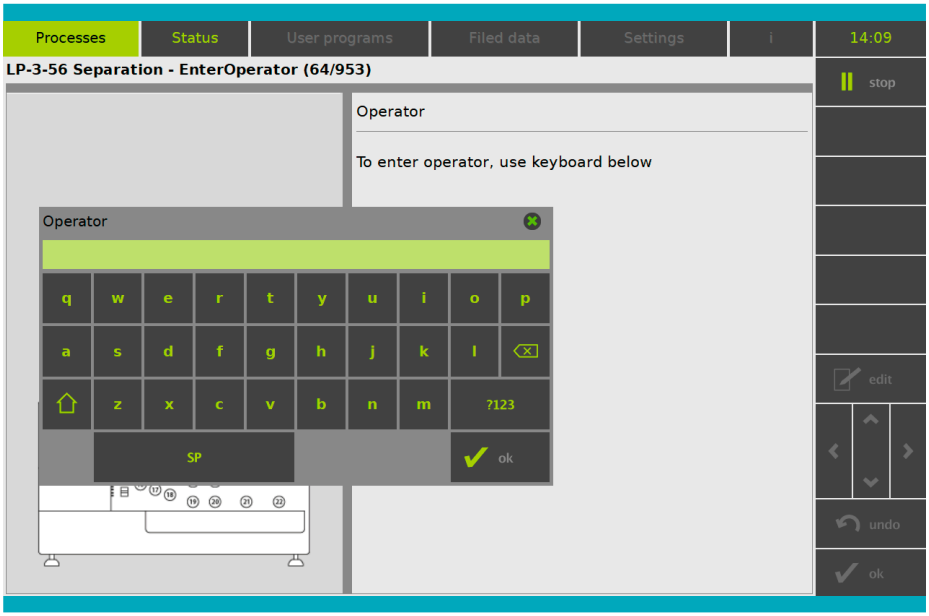


Screen 7.2: Self test

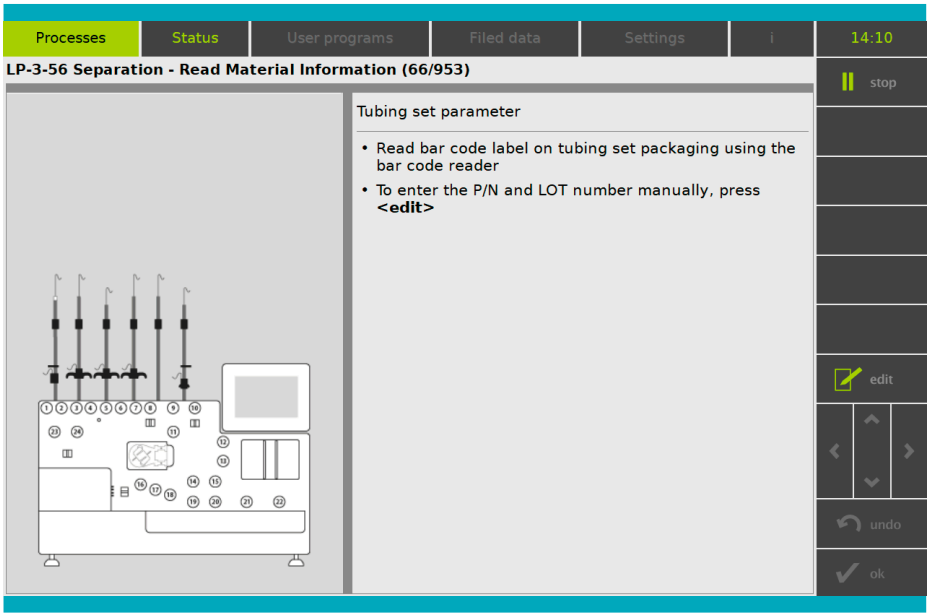
7.2 Parameter input and use case selection

Multiple parameters must be entered for the process either with the barcode reader connected to the CliniMACS Prodigy or the keyboard shown on the screen. Tap <ok> to confirm each entry. All entered parameters are saved in the process-related protocol.

Within the next steps of the process (see Screen 7.3 and Screen 7.4), enter information related to the operator and CliniMACS Prodigy TS 320. For the manual entry of capital letters tap <⇧>, for space tap <SP>, for numbers tap <?123>, and for backspace tap <⌫>.

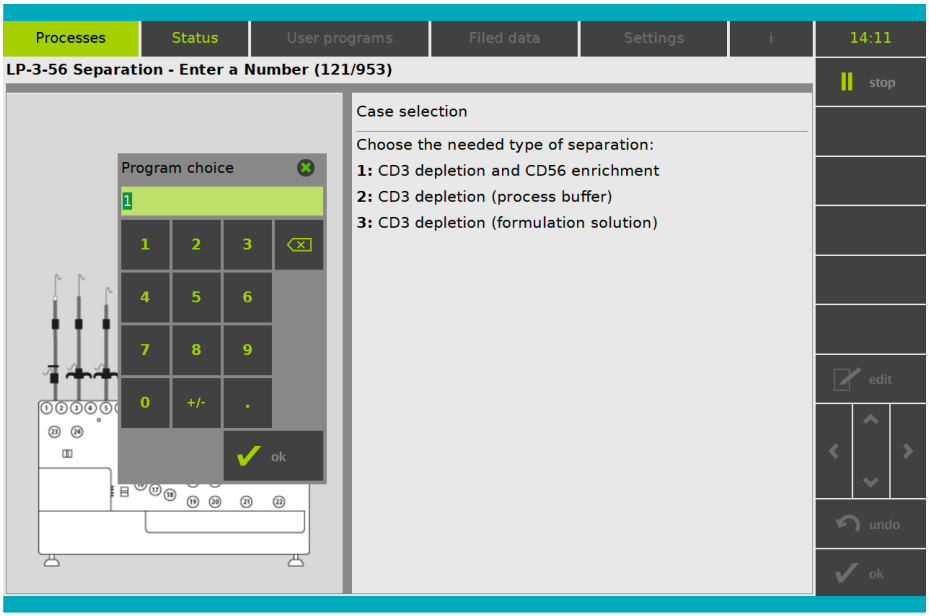


Screen 7.3: Entry of operator-related information



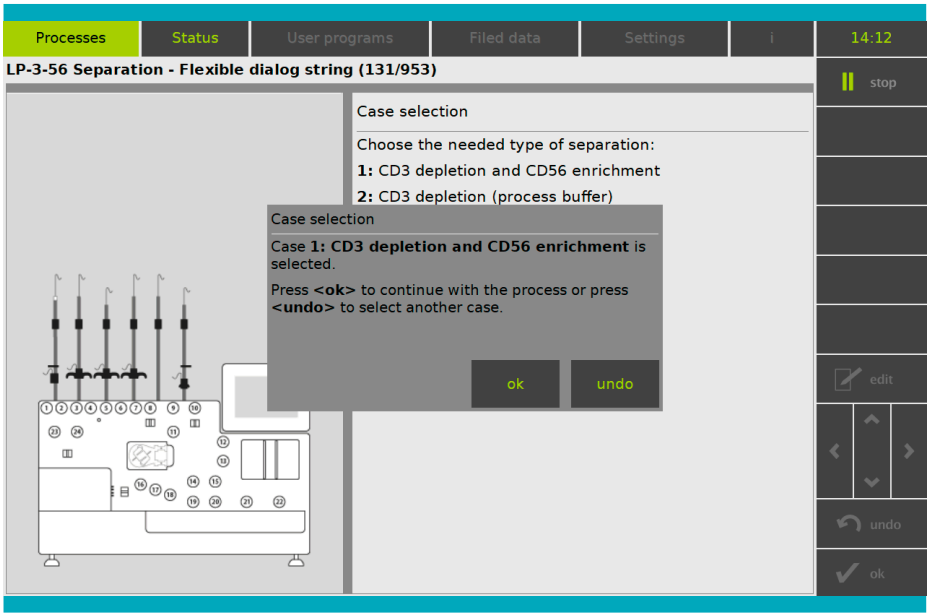
Screen 7.4: Entry of CliniMACS Prodigy TS 320 part number (P/N) and LOT number

Read the barcode label on the tubing set label or tap <edit> to enter part number (P/N) and LOT number manually with the keyboard shown on the screen.



Screen 7.5: Use case selection

After parameter input, the user has to choose one of three use cases (see section 3.2 "Process"). This user manual describes the complete process using use case 1 (CD3 depletion and CD56 enrichment) as the default process (see Screen 7.5).



Screen 7.6: Process setup confirmation

Select the desired use case and tap <ok> to confirm the selection. Tap <undo> to return to the use case selection (see Screen 7.6).

7.3 Tubing set installation

7.3.1 Components of the CliniMACS Prodigy TS 320

The components of the CliniMACS Prodigy TS 320 are pre-assembled on a mounting sheet and provided in a sealed and sterilized package. All components of the tubing set are illustrated in Figure 7.1.

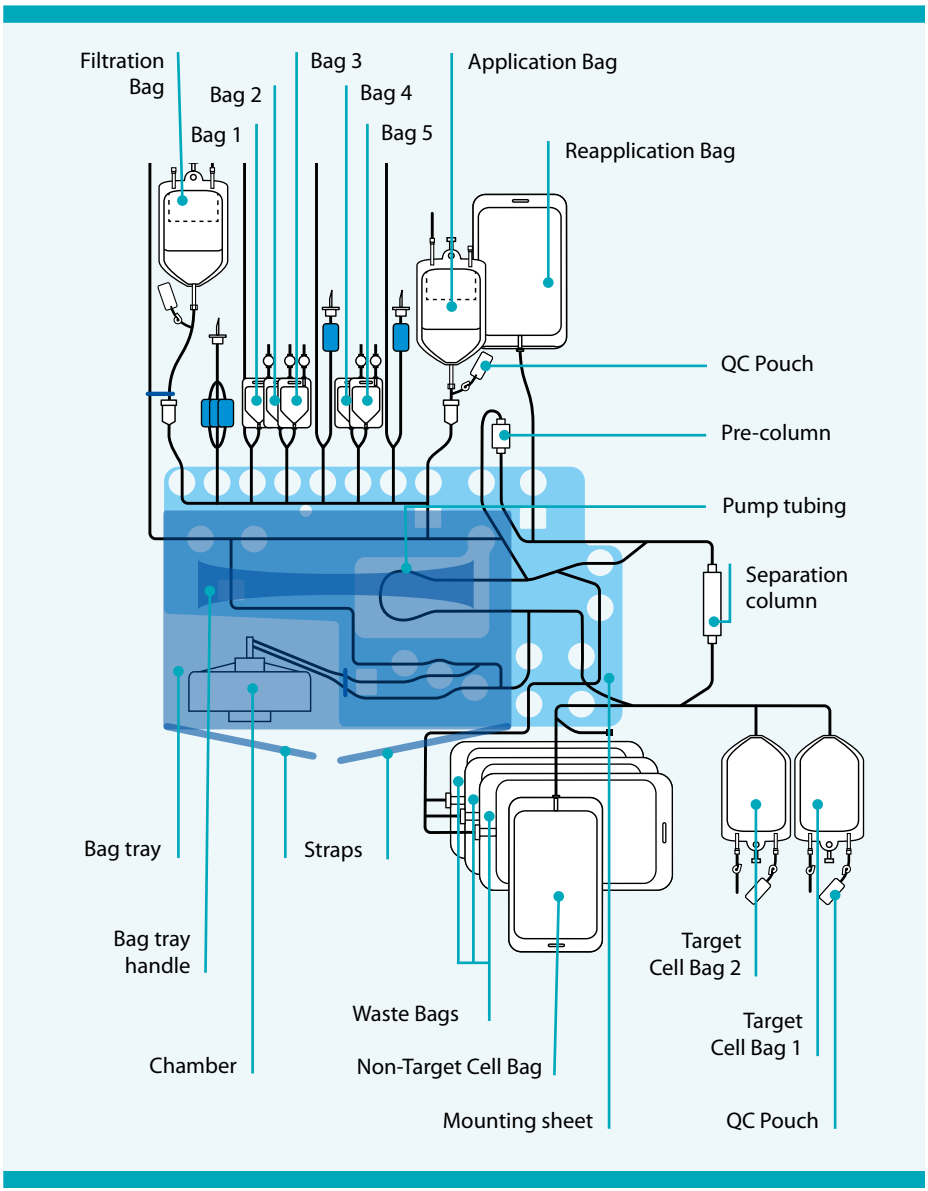


Figure 7.1: Components of the CliniMACS Prodigy TS 320

7.3.2 Installation steps

This section guides the user step by step through the installation of all tubing set components (see Screen 7.7 to Screen 7.27). Each screen shows the instructions supported by an image. Blinking and orange features in an image indicate areas of attention. At any step during the installation, tap <undo> to return to previos steps.

NOTICE

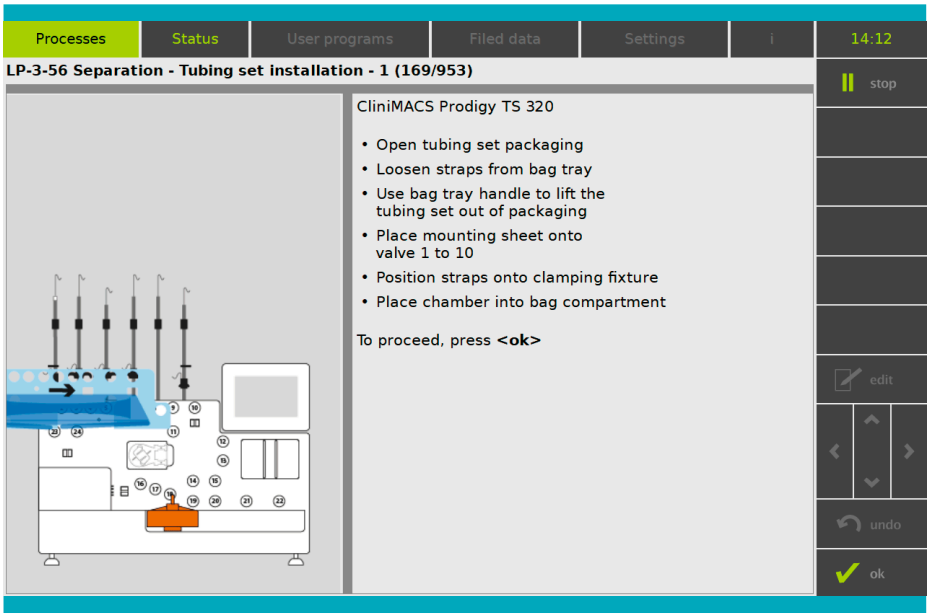
Risk of damage to the instrument. Overloading the bag hangers can damage the instrument. The carrying capacity of a single bag hanger is 5 kg.

- Do not overload the bag hangers.

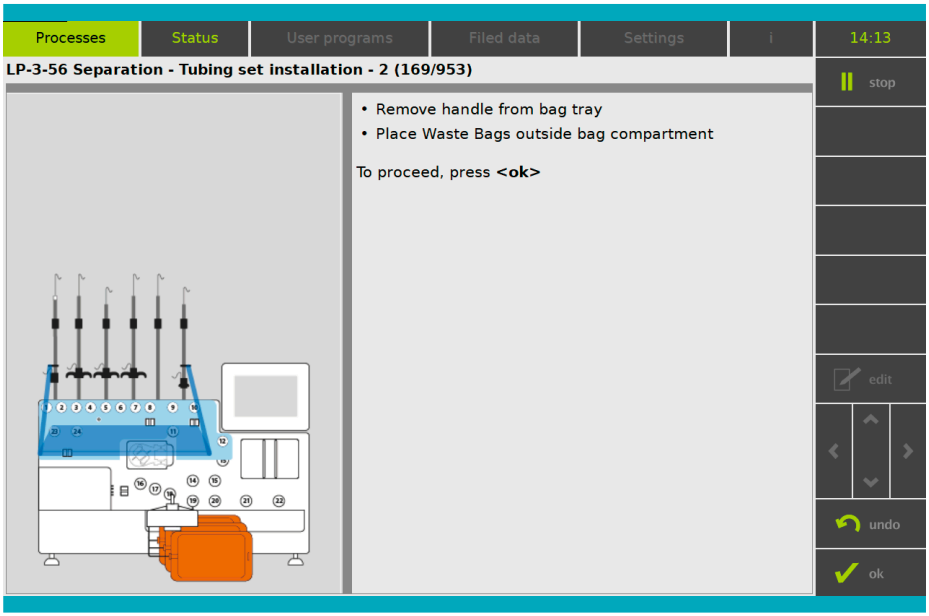
⚠ WARNING

Risk of contamination. Damaged packaging indicates that the tubing set may no longer be sterile and therefore must not be used.

- Carefully inspect the packaging for damage, puncture or tears. Use the tubing set only if package is undamaged and sealed.



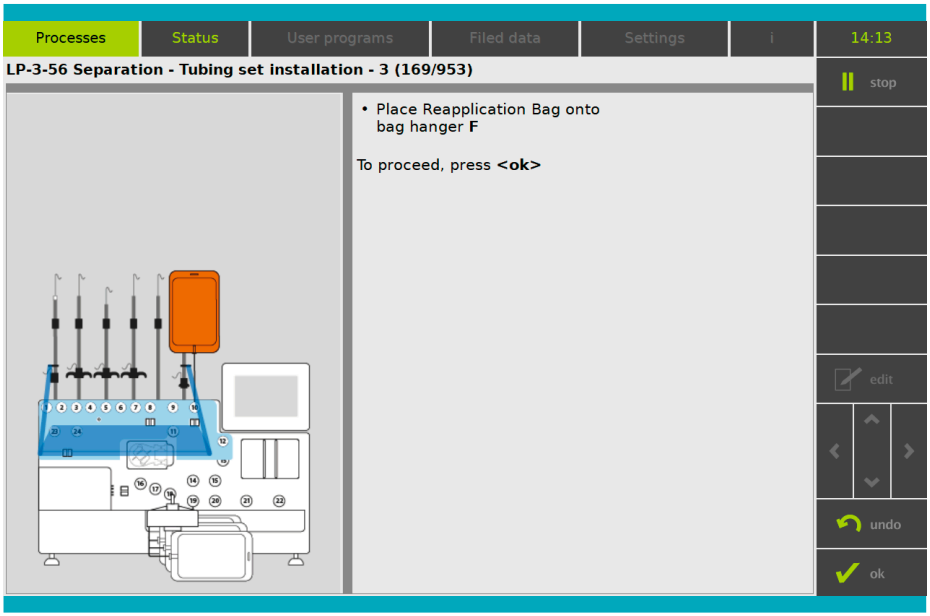
Screen 7.7: Installation of bag tray and mounting sheet onto the instrument



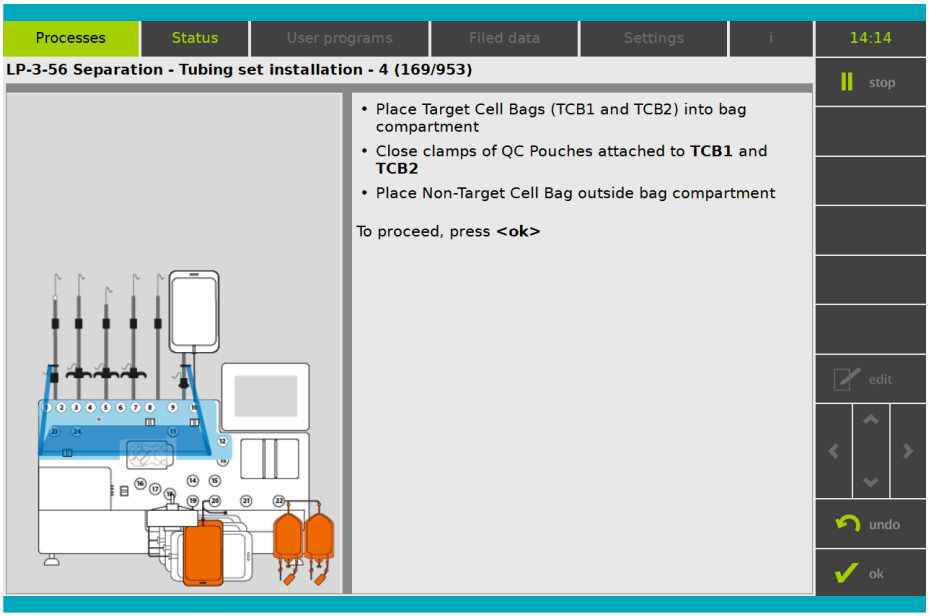
Screen 7.8: Placement of the three Waste Bags

IMPORTANT

The Waste Bags must be safely placed outside of the bag compartment on a plain surface next to or below the CliniMACS Prodigy.



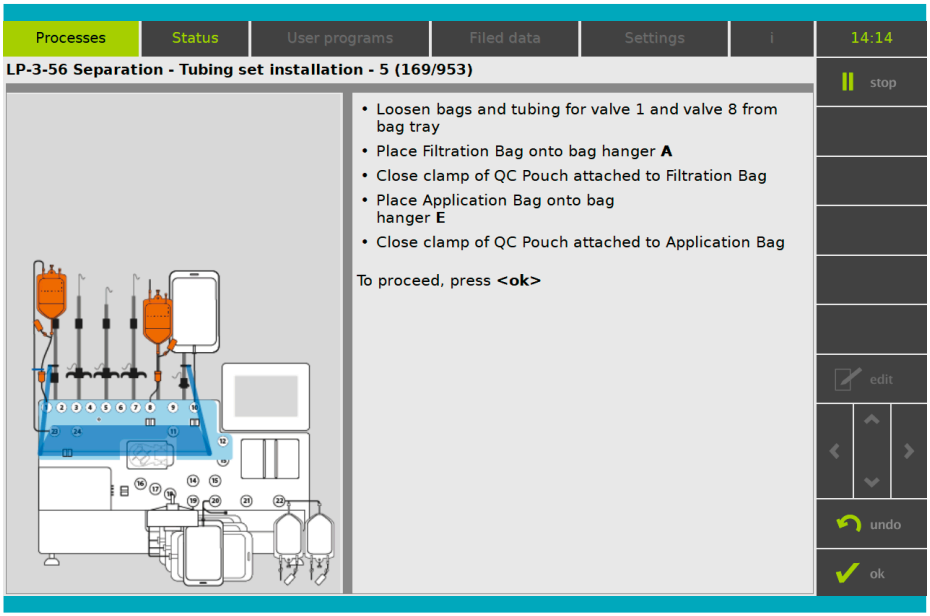
Screen 7.9: Placement of Reapplication Bag



Screen 7.10: Positioning of Target Cell Bags (TCB1 and TCB2) and Non-Target Cell Bag

IMPORTANT

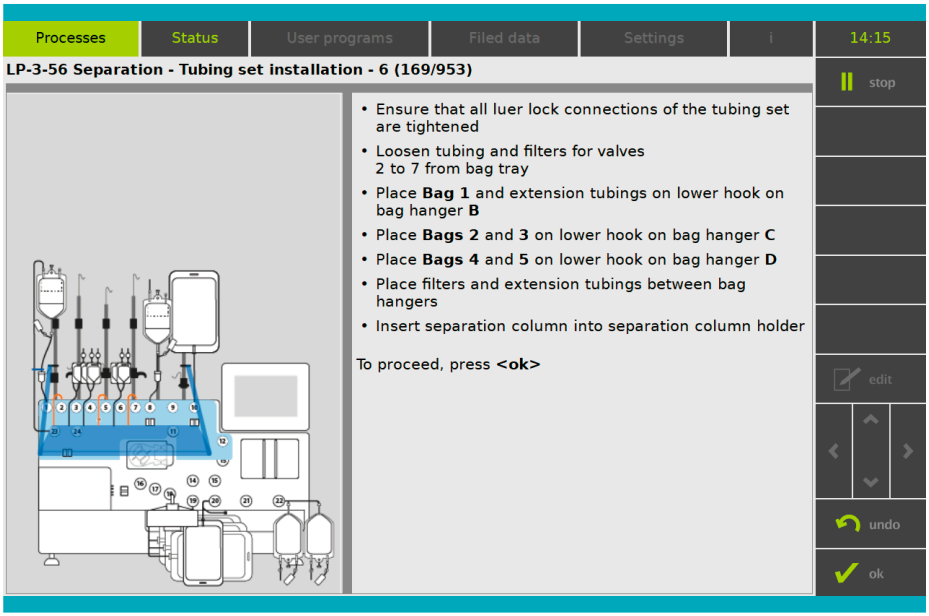
Ensure that the clamps on Target Cell Bag 2 and on the QC Pouches, which are attached to the Target Cell Bags, are properly closed.



Screen 7.11: Positioning of Filtration Bag and Application Bag

IMPORTANT

Ensure that the clamps on the QC Pouches, which are attached to the Filtration Bag and the Application Bag, are properly closed.



Screen 7.12: Attachment of Bags 1–5 and insertion of separation column

IMPORTANT

Hang the bags for the CliniMACS Reagents on the corresponding hooks.

Figure 7.2 shows how to insert the separation column into the column holder of the magnet unit. Hold the top and the bottom part of the column between thumb and index finger. The column label should be facing the user. Carefully insert the column into the column holder. Ensure that no tubing is pinched in between the column and the column holder.

⚠ WARNING

Risk of injury. Do not try to insert the separation column into the separation column holder or to remove the separation column from there in case the magnet unit is switched on.

- Contact Miltenyi Biotec Technical Support for assistance if required.

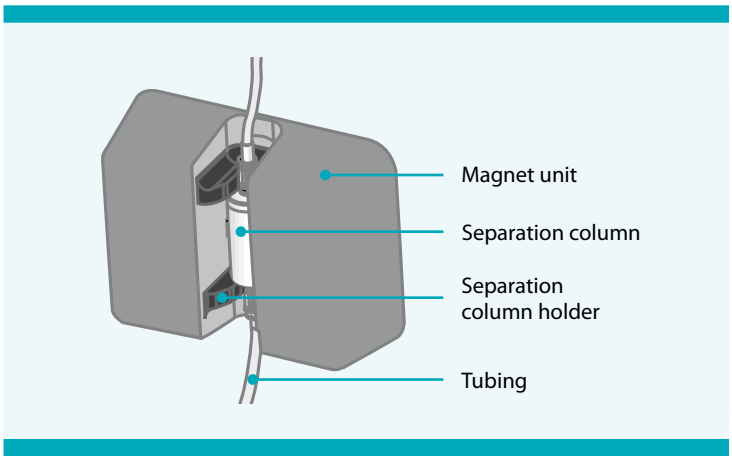
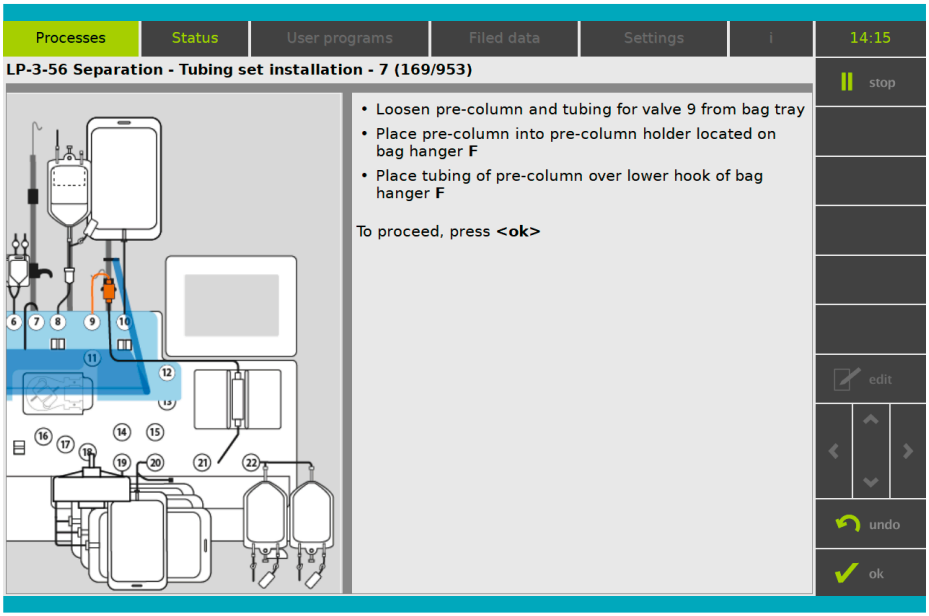


Figure 7.2: Separation column inserted into magnet unit



Screen 7.13: Insertion of the pre-column

Figure 7.3 shows how to hang the tubing over the lower hook on the bag hanger (F).

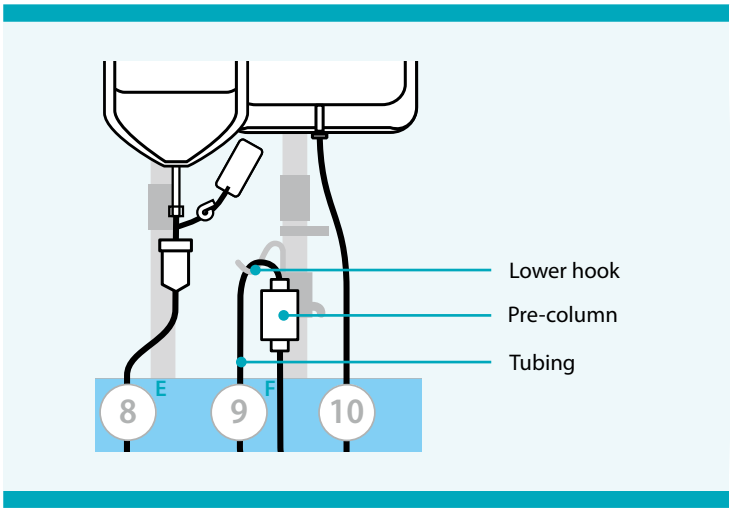
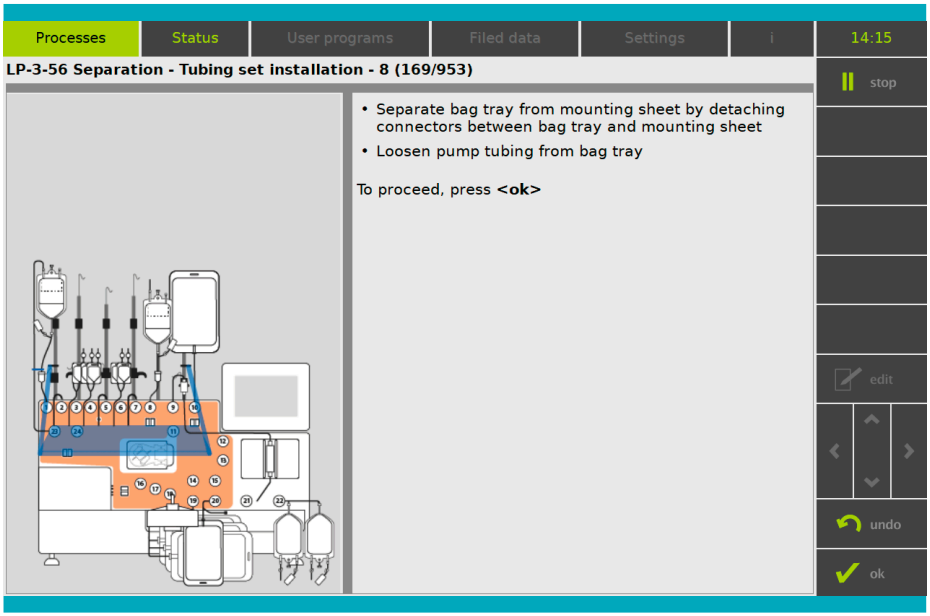
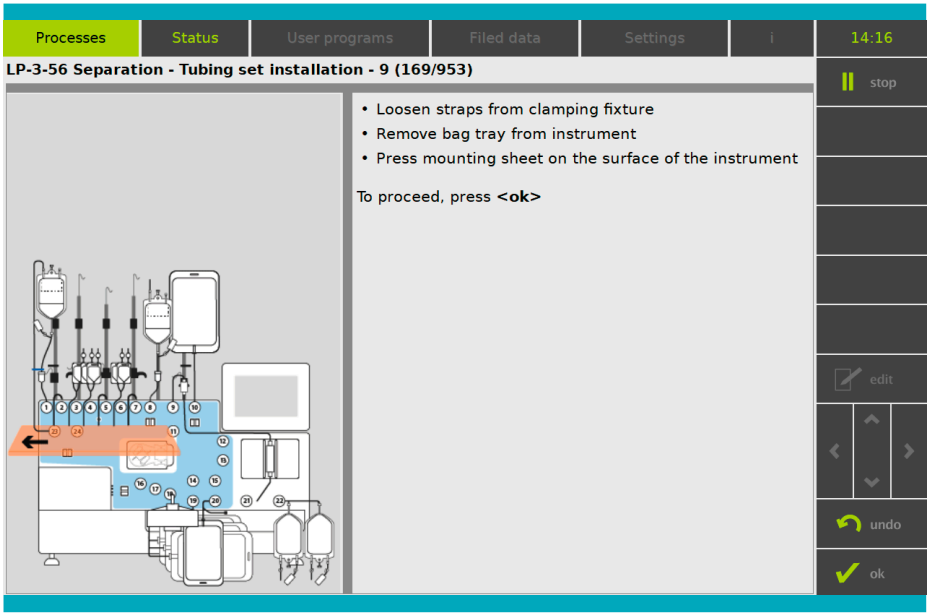


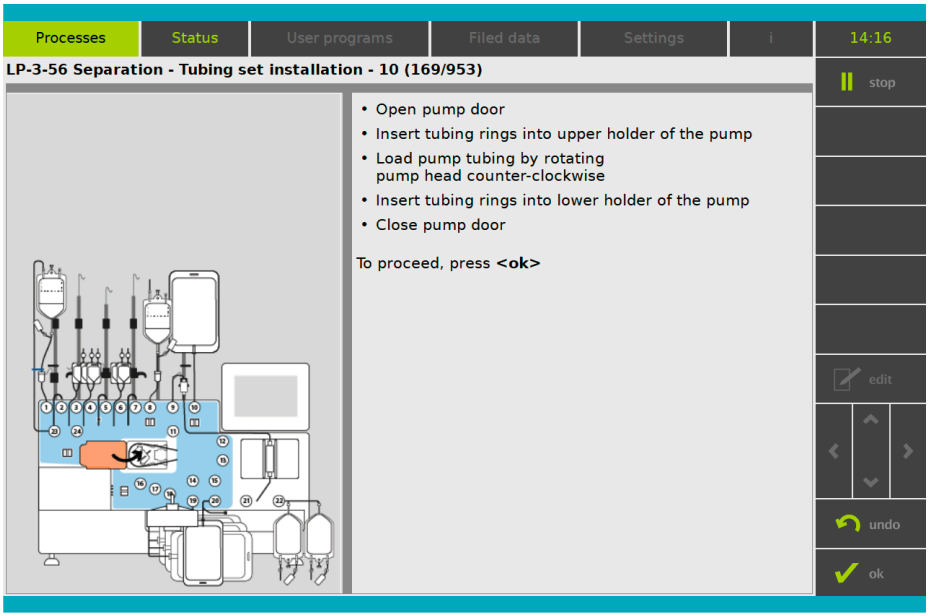
Figure 7.3: Guidance of pre-column tubing



Screen 7.14: Separation of bag tray from mounting sheet



Screen 7.15: Removal of bag tray from instrument



Screen 7.16: Insertion of pump tubing into pump

Figure 7.4 shows how to insert the pump tubing into the pump.

1. Insert the upper tubing rings in the intended cavities.
2. Rotate the pump head counterclockwise until the tubing is threaded between both sets of tubing guide pins of the pump head.
3. Then insert the lower tubing rings in the intended cavities.
4. Ensure that the pump tubing is not pinched between the guide pins.
5. Turn the pump head clockwise and counterclockwise to ensure the pump head moves freely.

To unload the tubing remove the lower end of the tubing from the cavities while turning the pump head clockwise until the tubing is released.

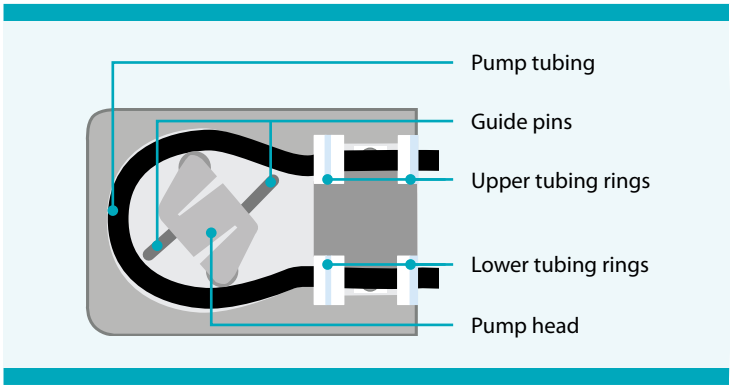
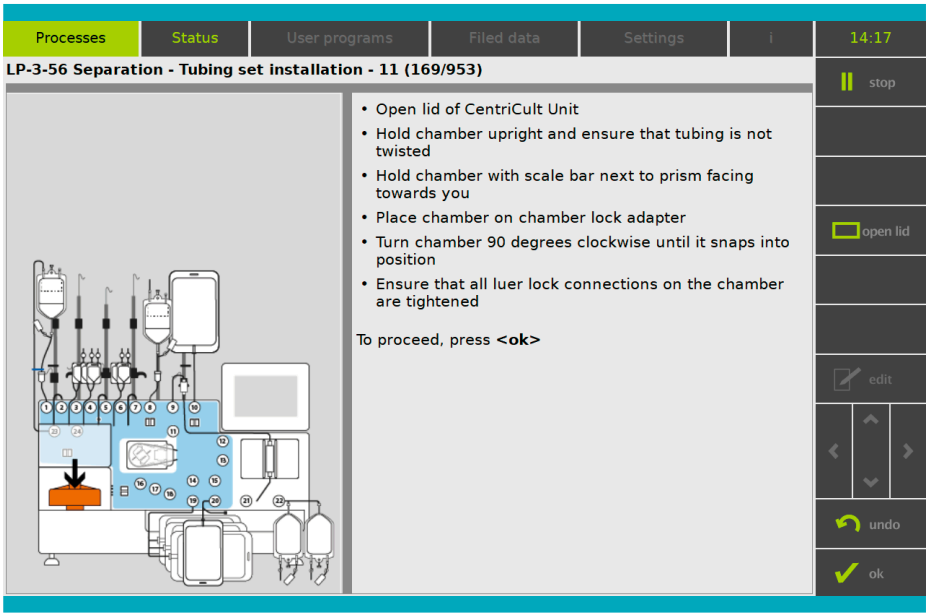


Figure 7.4: Pump tubing inserted into pump



Screen 7.17: Installation of chamber into CentriCult Unit

Figure 7.5 shows the components of the CentriCult unit.

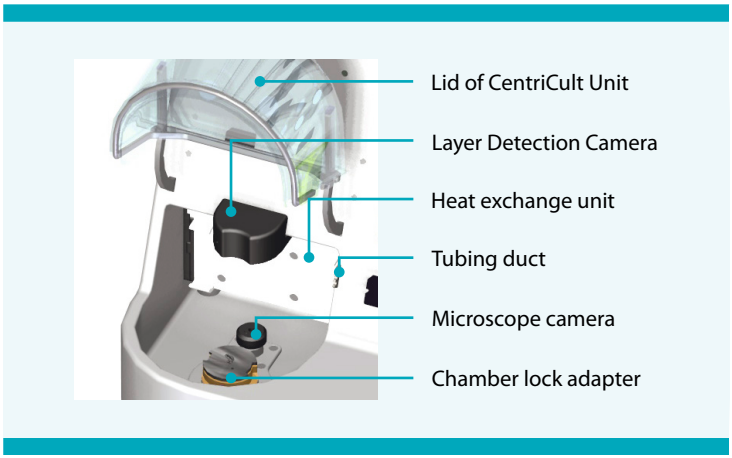


Figure 7.5: Components of CentriCult Unit

The CentriCult Unit lid unlocks automatically during this process step. If the lid does not unlock automatically, tap <open lid> on the tool bar.

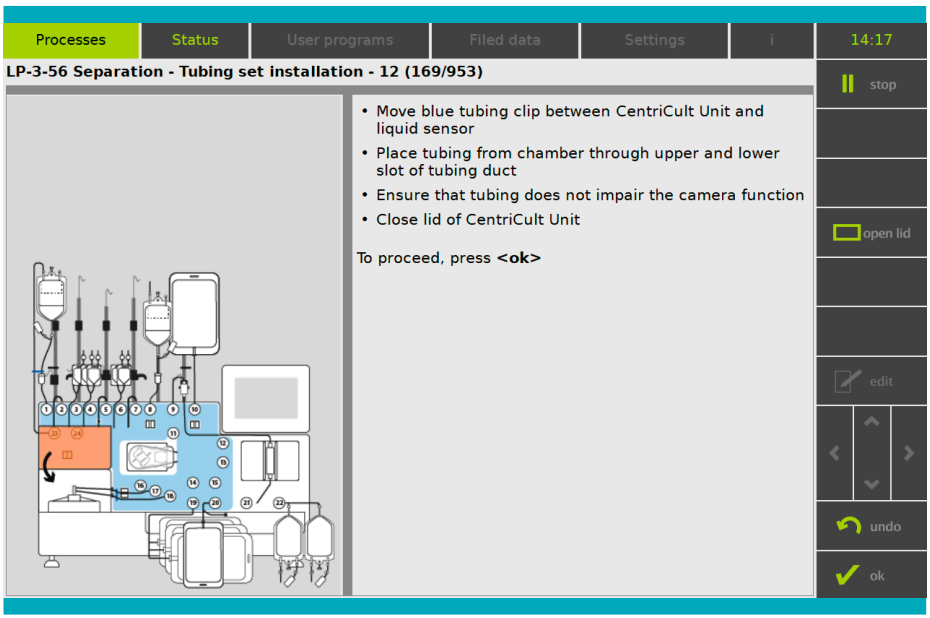
IMPORTANT

The chamber has a scale bar on its lid. This scale bar must point towards the user when placed on the chamber lock adapter. Before closing the lid, ensure that no tubing is pinched by the lid.

NOTICE

Risk of process delay. An incorrectly installed chamber tubing can cause a process delay.

- Before positioning the chamber onto the chamber lock adapter ensure that the tubing attached to the chamber is in a parallel position and not twisted or bent. The chamber must not be detachable from the chamber lock adapter once it is snapped into position.



Screen 7.18: Installation of chamber-associated tubing

Figure 7.6 illustrates how to insert the two tubing lines of the chamber through the tubing duct. Ensure that the tubing is not twisted or pinched by the lid of the CentriCult Unit.

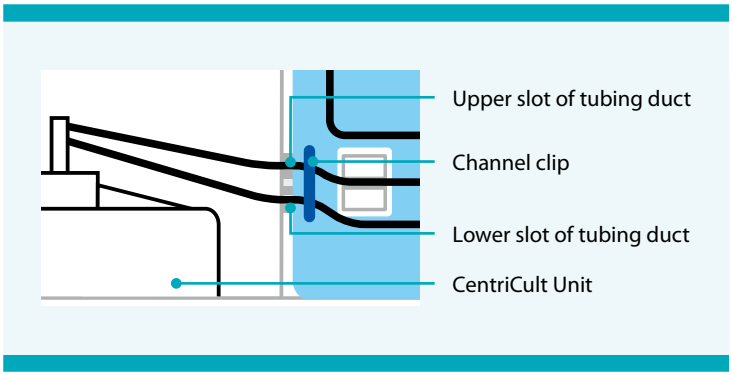
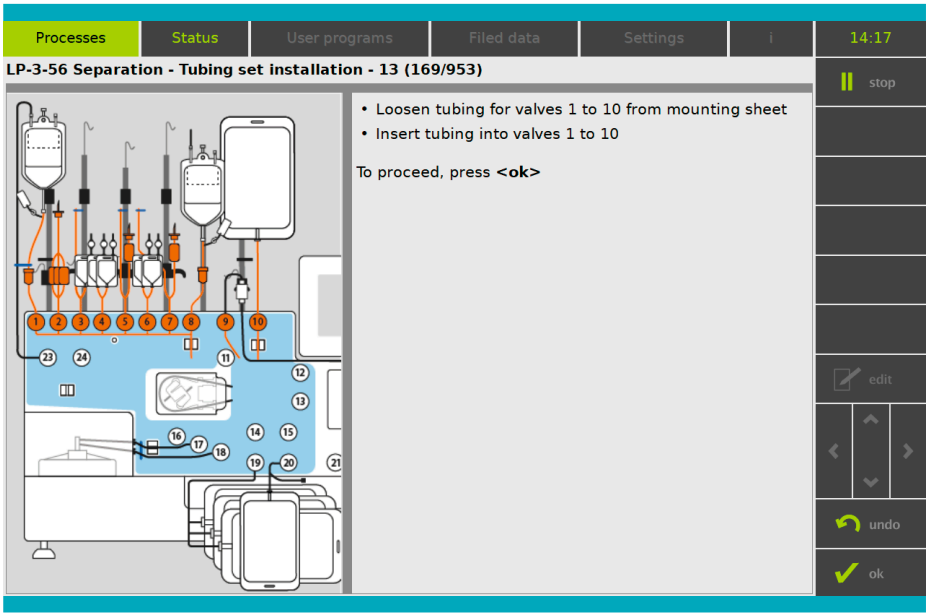


Figure 7.6: Guidance of tubing through tubing duct



Screen 7.19: Insertion of tubing into valves 1 – 10

Figure 7.7 shows how to correctly insert the tubing into the respective valves. Insert the tubing only into open valves (when the button is pressed down). Otherwise, the tubing will not fit correctly. If a tubing position has to be adjusted, press the valve button to open the valve before adjustment.

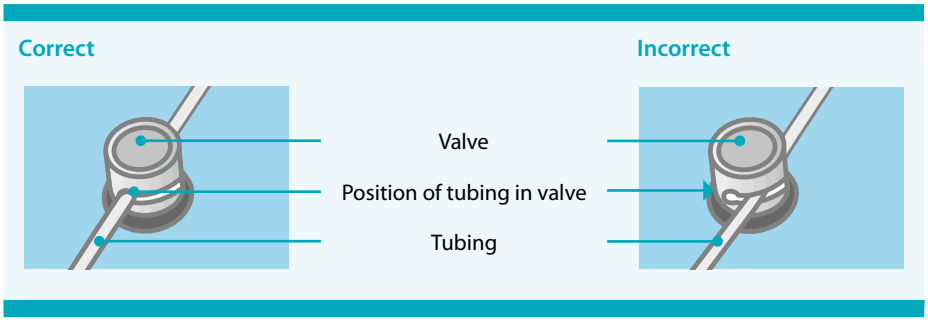
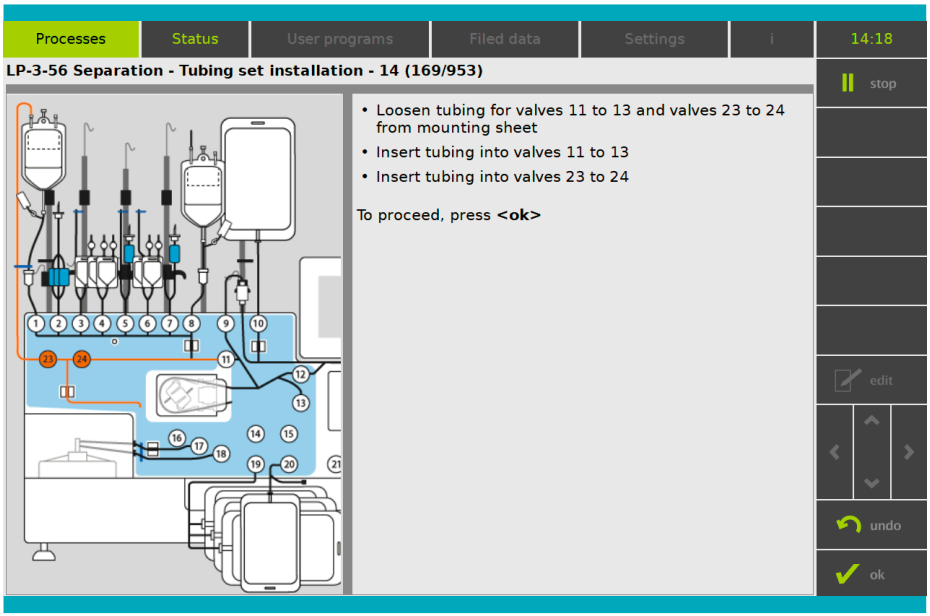


Figure 7.7: Insertion of tubing into valves



Screen 7.20: Insertion of tubing into valves 11 – 13 and 23 – 24

Figure 7.8 shows how to correctly insert the tubing into valve 12 and 13.

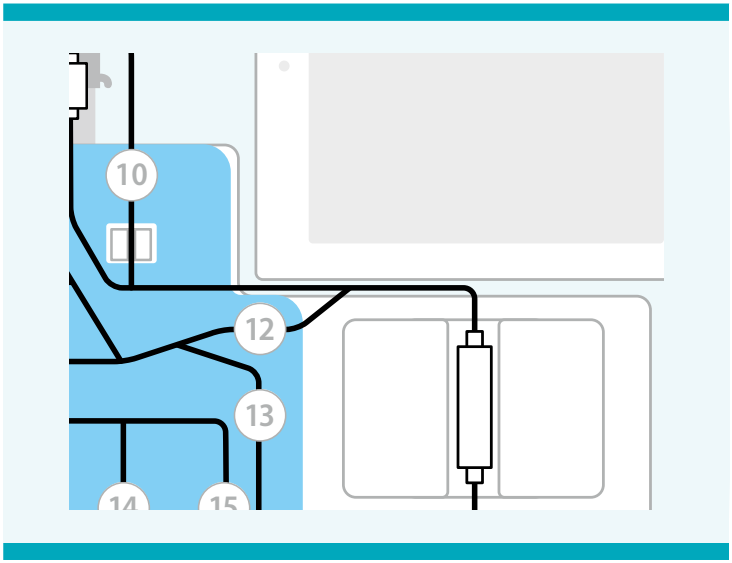
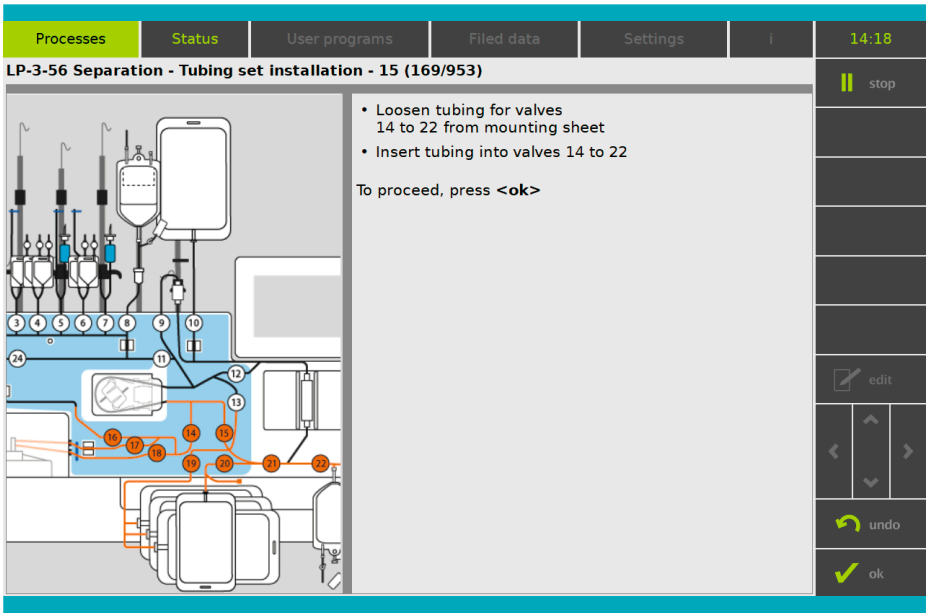
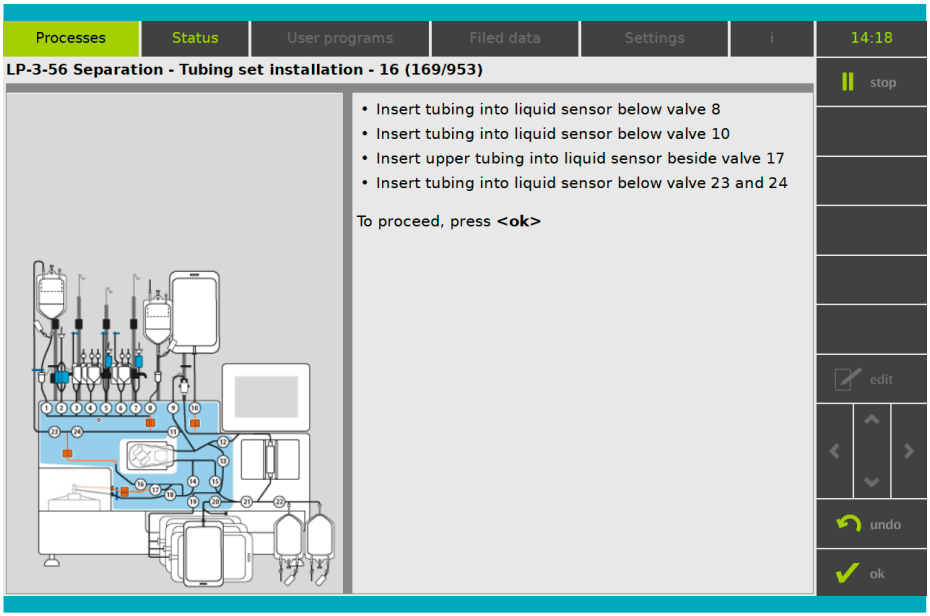


Figure 7.8: Guidance of tubing for separation column and valves 12 and 13



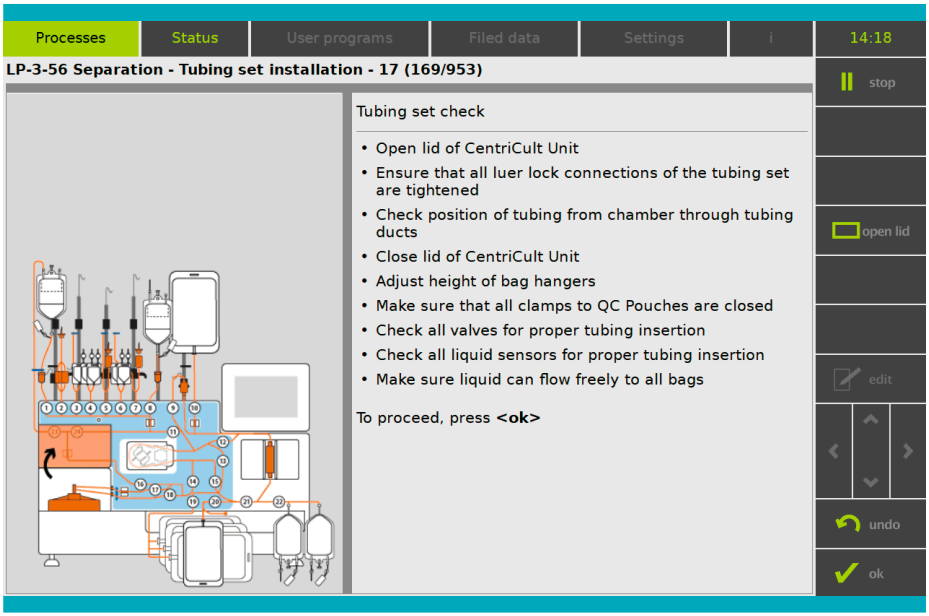
Screen 7.21: Insertion of tubing into valves 14 – 22



Screen 7.22: Insertion of tubing into liquid sensors

IMPORTANT

To ensure a proper operation of the liquid sensor, both, the liquid sensor and the outside of the tubing must be dry. If any liquid is present on the liquid sensor, dry the area with a soft, lint-free cloth.



Screen 7.23: Final check of tubing set installation

IMPORTANT

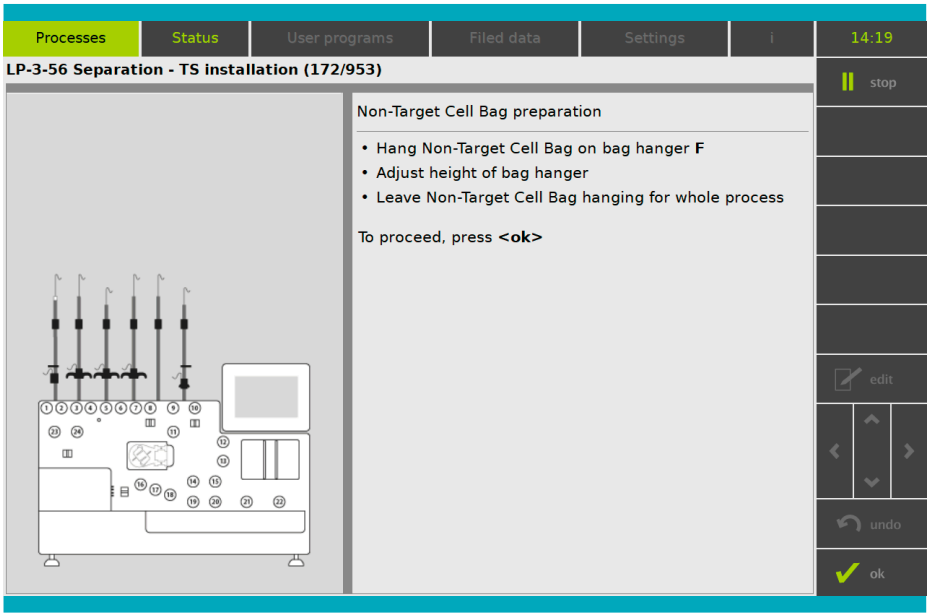
Review all tubing for kinks or severe bending that could restrict the flow of liquid through the tubing set and verify the tightness of all Luer Lock connections of the tubing set. If a tubing position has to be adjusted, press the valve button to open the respective valve beforehand (see Figure 7.7).

The CentriCult Unit lid unlocks automatically during this process step. If the lid does not unlock automatically, tap **<open lid>** on the tool bar. Furthermore, it is possible to remove and re-insert the chamber at this step, (e.g., if the chamber tubing has been twisted during installation).

In case the lid cannot be opened, contact Miltenyi Biotec Technical Support.

If necessary, raise or lower the bag hangers to adjust the height. Ensure that the bags are positioned high enough to prevent severe bending of the tubing and low enough to avoid tubing or connections being stretched. In addition, verify the tightness of all Luer Lock connections on the tubing set.

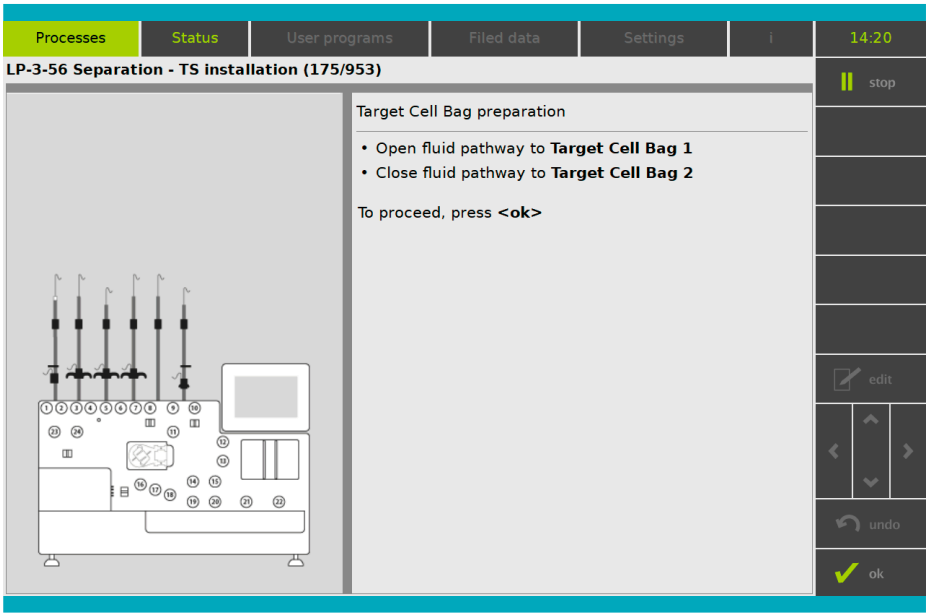
When the tubing set installation is completed, all valves are automatically opened and closed twice to verify proper functionality. In addition, the forward and backward movement of the magnet is tested. If a valve or the magnet does not operate correctly, contact Miltenyi Biotec Technical Support.



Screen 7.24: Attach Non-Target Cell Bag to bag hanger

IMPORTANT

When processing use case 1 (depletion of CD3-positive cells followed by enrichment of CD56-positive cells) the Non-Target Cell Bag must hang on bag hanger F during the whole separation.



Screen 7.25: Target Cell Bag preparation

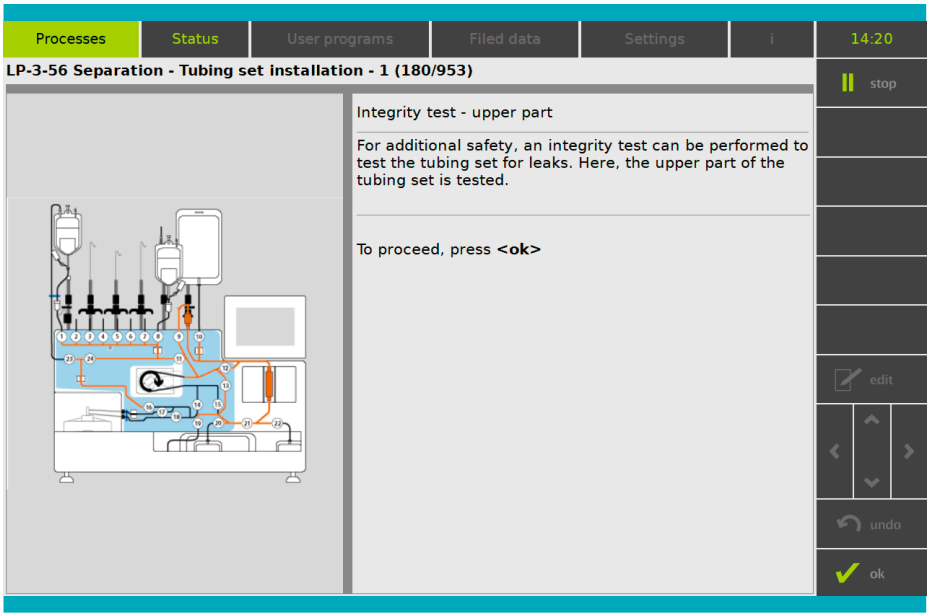
IMPORTANT

Close clamp on fluid pathway to Target Cell Bag 2 to assure collection of target cells in Target Cell Bag 1.

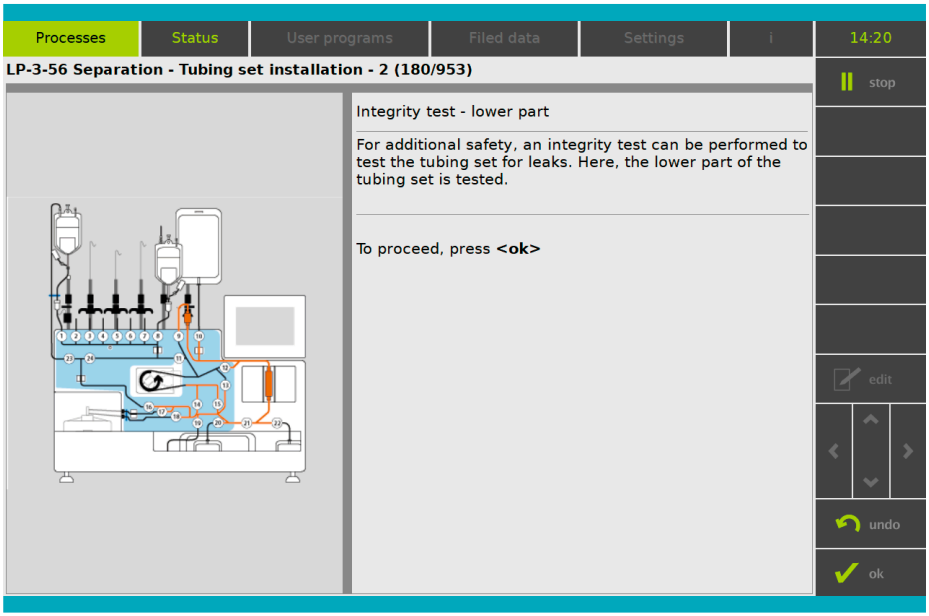
IMPORTANT

For additional safety, an integrity test must be performed to inspect the tubing set for potential leaks. The test consists of two automated sequences that apply controlled overpressure separately to the upper and lower part of the tubing set.

Follow the instructions on the screens to start the integrity test for the upper and lower part of the tubing set. It is possible, but clearly not recommended, to tap <no> on the display to skip the integrity test.



Screen 7.26: Integrity test for upper part



Screen 7.27: Integrity test for lower part

⚠ WARNING

Risk of contamination. A failed integrity test may indicate a potential leakage in the tubing set.

- If a tubing set fails the integrity test, carefully verify that all tubing is correctly inserted into the appropriate valves.
- Also check for visible leaks in the tubing set.
- In case of a failed integrity test, both testing sequences can be repeated.
- Repeat the integrity test after verification of proper tubing set installation and absence of any leaks.

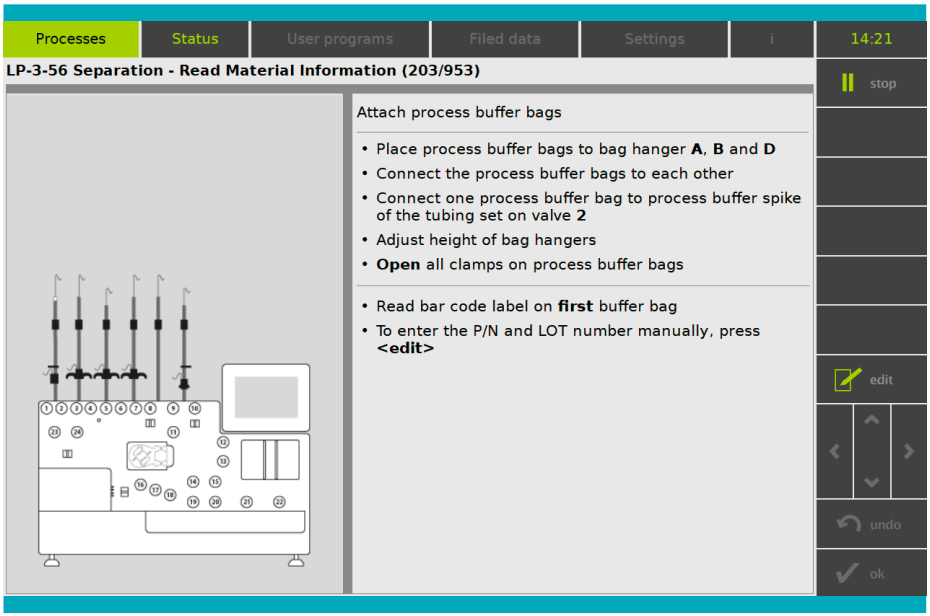
Contact Miltenyi Biotec Technical Support for assistance, if required.

Do not use the tubing set, if it is not possible to successfully pass the integrity test. Contact Miltenyi Biotec Technical Support for detailed information on complaint filing for a defective product.

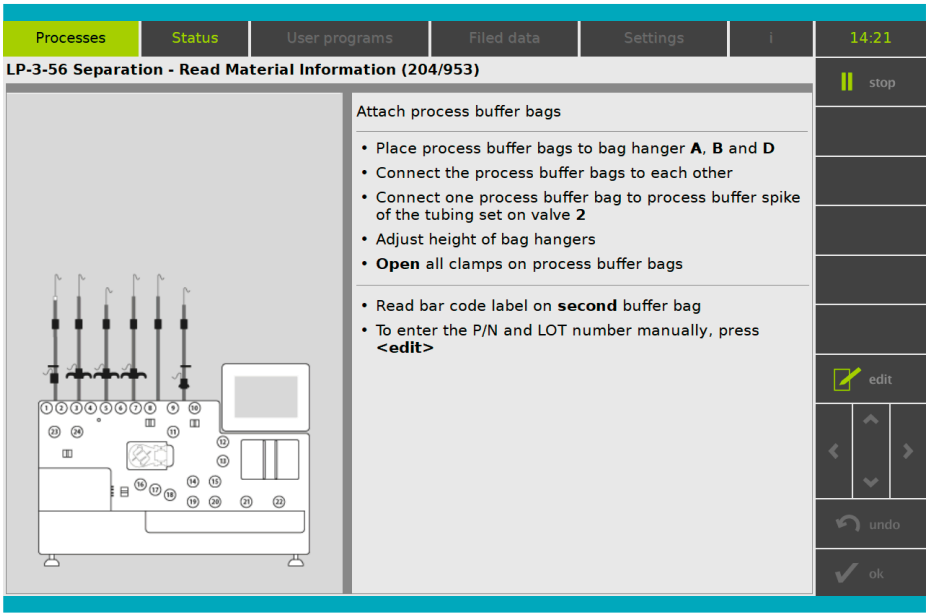
7.4 Tubing set priming

7.4.1 Connection of process buffer, formulation solution, and rinsing solution

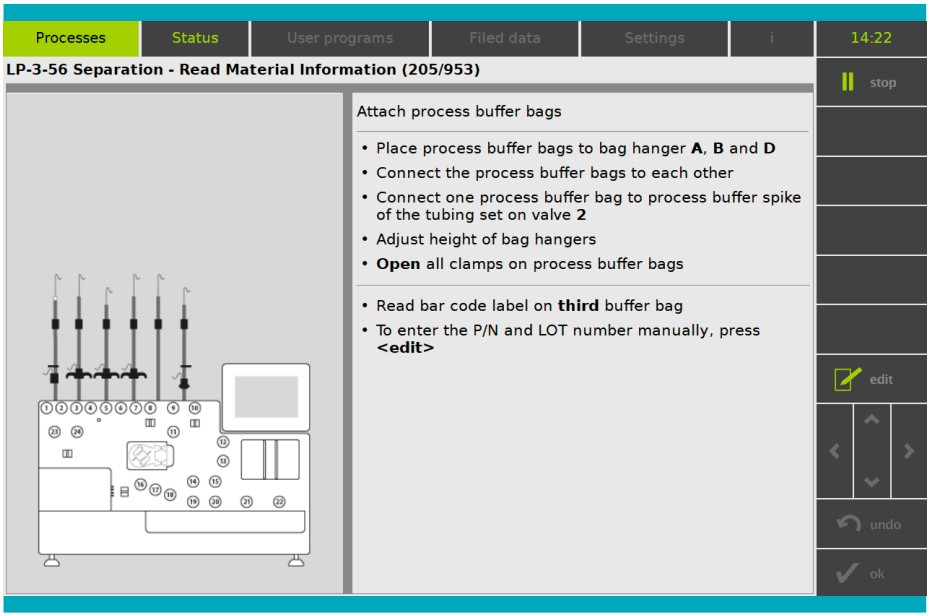
Refer to chapter 6 ´Preparative steps´ of this user manual for the preparation of the process buffer, formulation solution, and rinsing solution.
Screen 7.28 to Screen 7.36 guide the user through the priming phase.



Screen 7.28: Connection of first process buffer bag



Screen 7.29: Connection of second process buffer bag

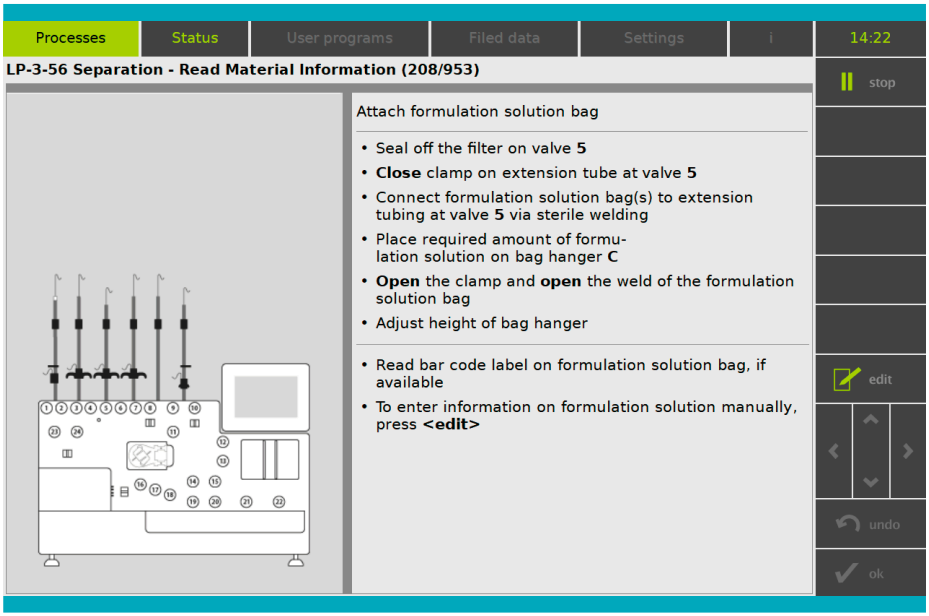


Screen 7.30: Connection of third process buffer bag

IMPORTANT

Use a plasma transfer set to connect the process buffer bags to each other. Close the clamps during the connection to each other. To ensure a fluid run, adjust the height of bag hanger A, B, and D to the highest position.Position the three process buffer bags at the same height and put all clamps in the open position.

Read the barcode label on the process buffer bags with the barcode reader or tap <edit> to manually enter part numbers (P/N) and LOT numbers using the keyboard shown on the screen.

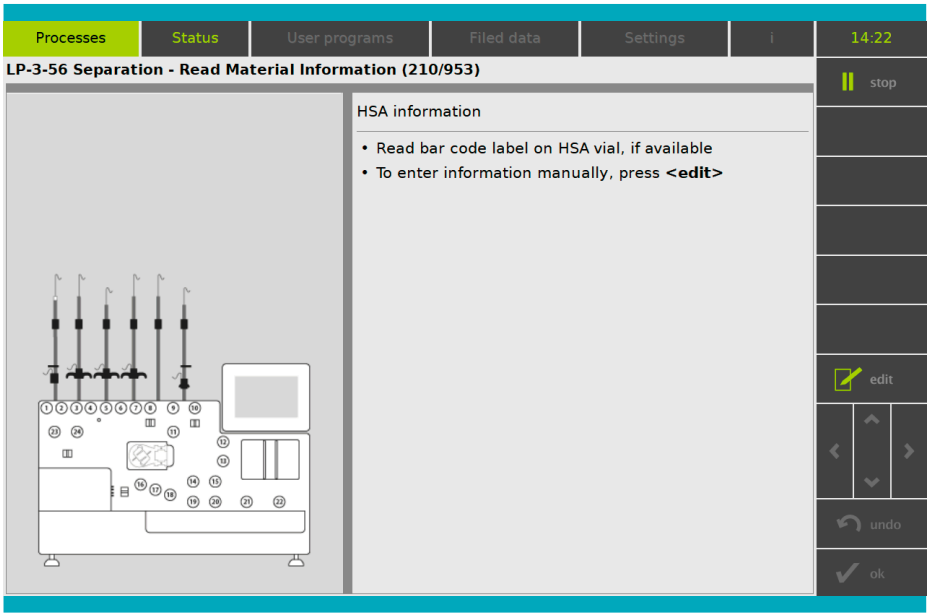


Screen 7.31: Connection of formulation solution bag

For the connection of the formulation solution bag to the tubing set line on valve 5, follow the institution's standard operation procedures. Connect the bag with a sterile docking device for sterile tubing connections.

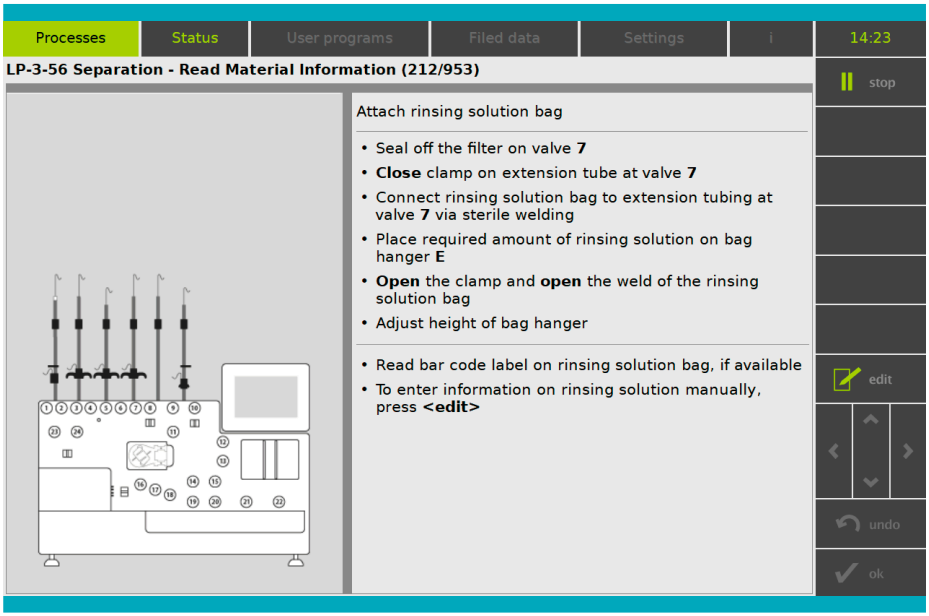
Read the barcode label on the formulation solution bag in case a process buffer is used. Alternatively, tap <edit> to enter part number (P/N) and LOT number manually with the keyboard shown on the screen.

Refer to chapter 6 ´Preparative steps´ of this user manual for the preparation of process buffer and formulation solution.



Screen 7.32: Entry of HSA information

Tap <edit> to enter information regarding the HSA.



Screen 7.33: Connection of rinsing solution bag

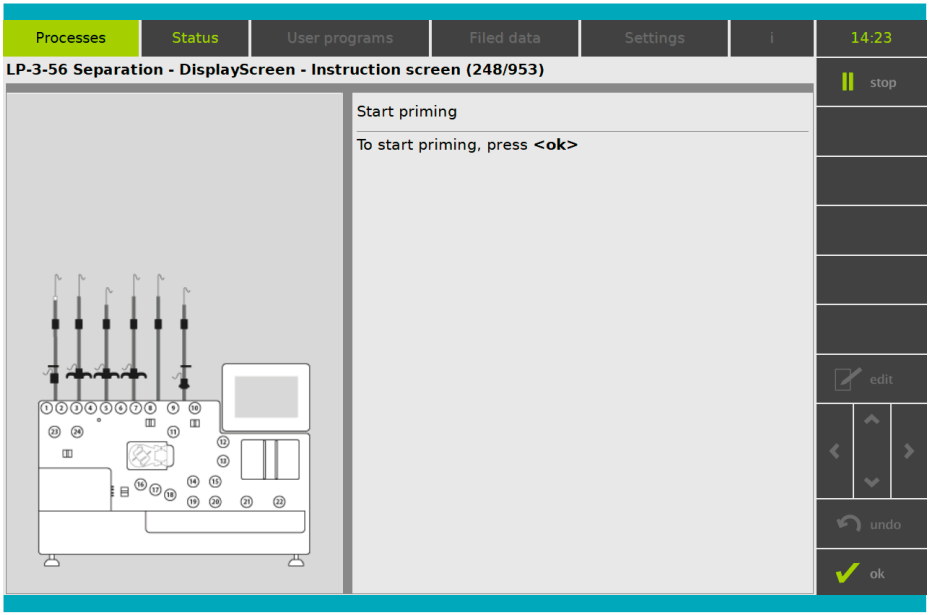
Before connecting the rinsing solution to the extension tube on valve 7, refer to section 6.4 ´Preparation of rinsing solution´. If necessary, the height of the bag hanger can be adjusted to the size of the bags by raising or lowering the hangers.
Ensure that the bags are positioned high enough to prevent severe bending of the tubing and that they are low enough to avoid the tubing or connections being stretched.

An overview of the positioning of the different bags on the bag hangers is provided below in Table 7.1.

Materials	Comments
A	Process buffer bag Filtration Bag
B	Process buffer bag
C	Formulation solution bag
D	Process buffer bag
E	Application Bag Rinsing solution bag
F	Reapplication Bag Non-Target Cell Bag

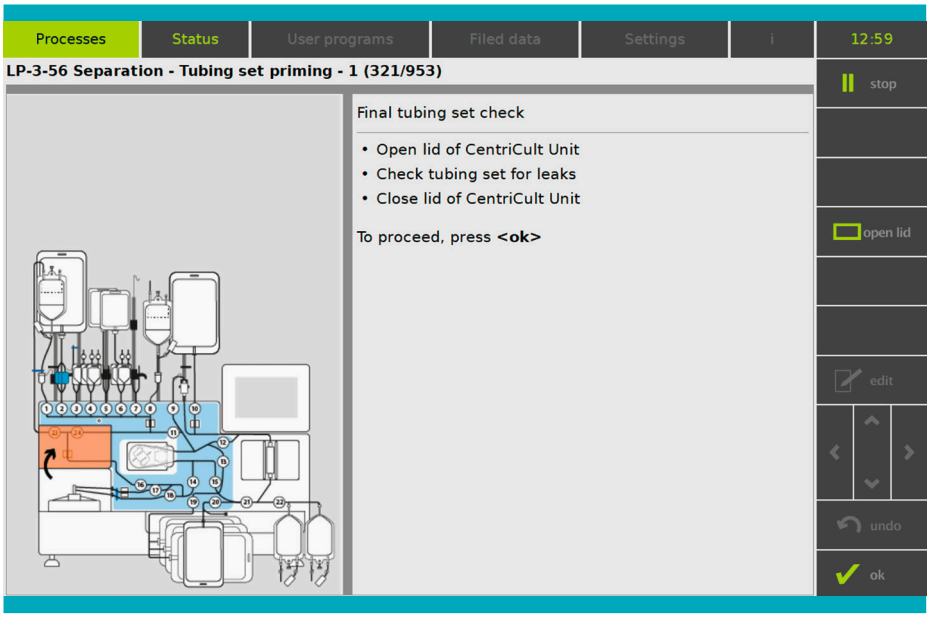
Table 7.1: Positions of bags

7.4.2 Priming phase



Screen 7.34: Start of priming phase

During the priming phase, the tubing set is filled with process buffer. The priming includes repeating cycles. The time for the priming phase is shown as a process bar on the screen.

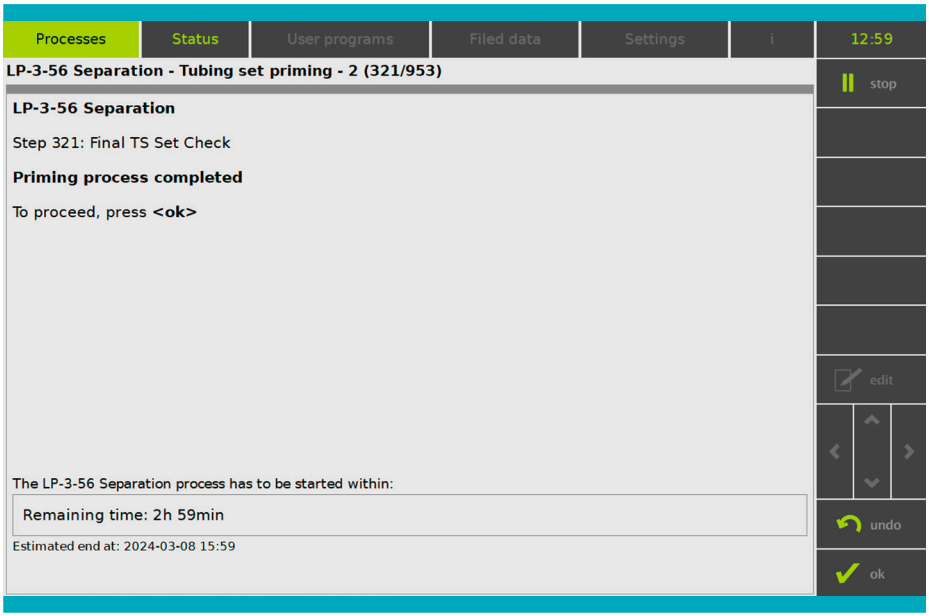


Screen 7.35: Final tubing set check after priming phase

IMPORTANT

When the priming phase is completed, check all bags, tubing, fittings, valves, chamber, and columns for the appearance of leaks or the presence of kinks that may block fluid pathways. All clamps of QC Pouches and the clamp on the Target Cell Bag 2 must be closed. Ensure that all other tubing set clamps are in the open position. If leaks are observed, inform Miltenyi Biotec Technical Support and do not use the tubing for the application. Restart the process with a new tubing set and buffers.

The CentriCult Unit lid unlocks automatically during this process step. If the lid does not unlock automatically, tap **<open lid>** on the tool bar. In case the lid cannot be opened, contact Miltenyi Biotec Technical Support.



Screen 7.36: End of priming phase

The screen is shown when the priming phase is completed.

Check if all components are available for the separation phase (CliniMACS CD3 Reagent, CliniMACS CD56 Reagent, IgG solution, and starting cell product).

7.5 Preparation for the automated separation process

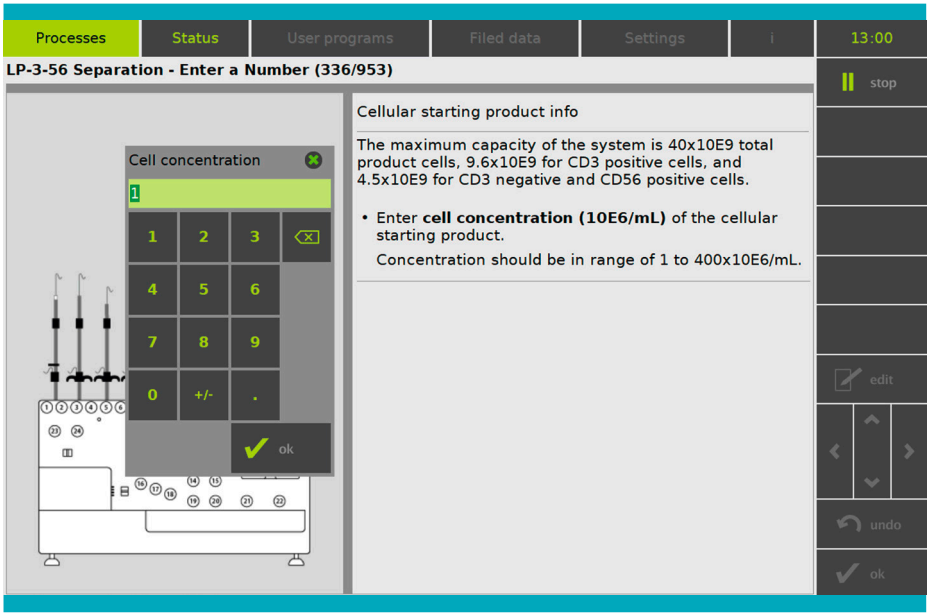
7.5.1 Parameter input

Screen 7.37 to Screen 7.46 guide the user through the preparation phase.

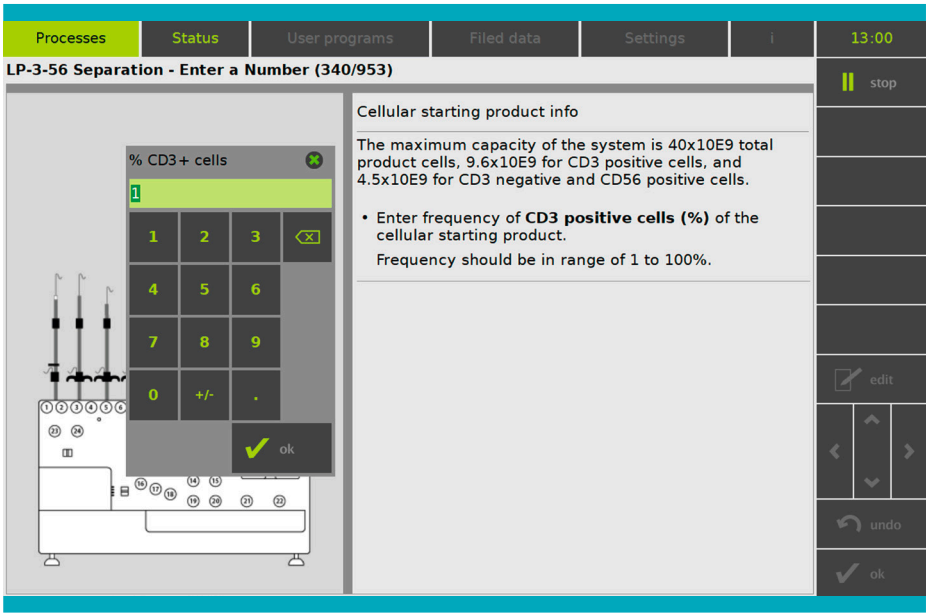
IMPORTANT
The volume of the starting cell product must be between 50 mL and 600 mL. The process capacity is 9.6×10^9 total CD3-labeled cells and 4.5×10^9 CD56-labelled cells from a total of 40×10^9 WBC using one vial of CliniMACS CD3 Reagent and CliniMACS CD56 Reagent, respectively.

Parameter input for CD3 depletion and CD56 enrichment

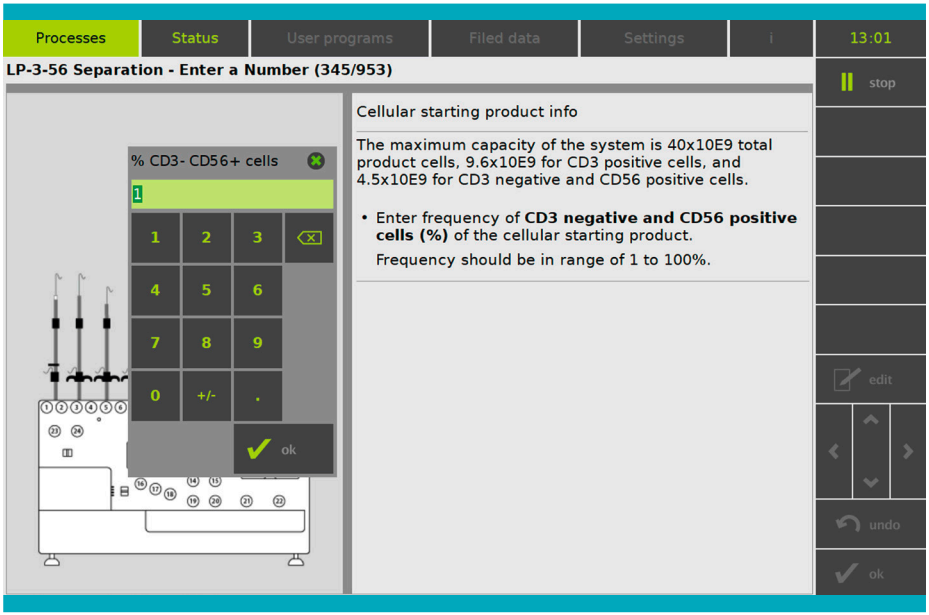
Enter the WBC concentration ($\times 10^6$/mL), frequency of CD3-positive cells (%), frequency of CD56-positive CD3-negative cells (%), and volume (mL) of the starting cell product that is going to be transferred into the Application Bag.



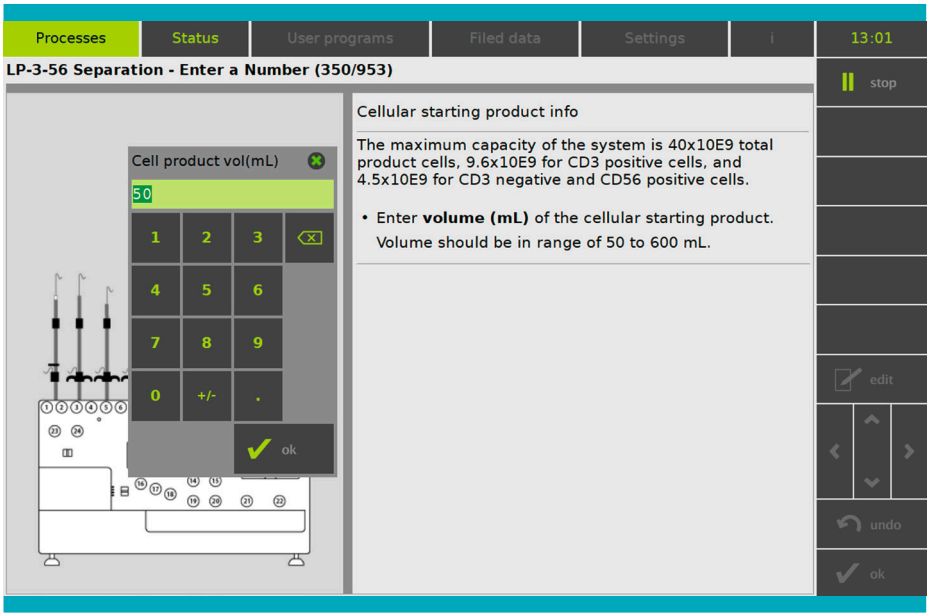
Screen 7.37: Entry of WBC concentration



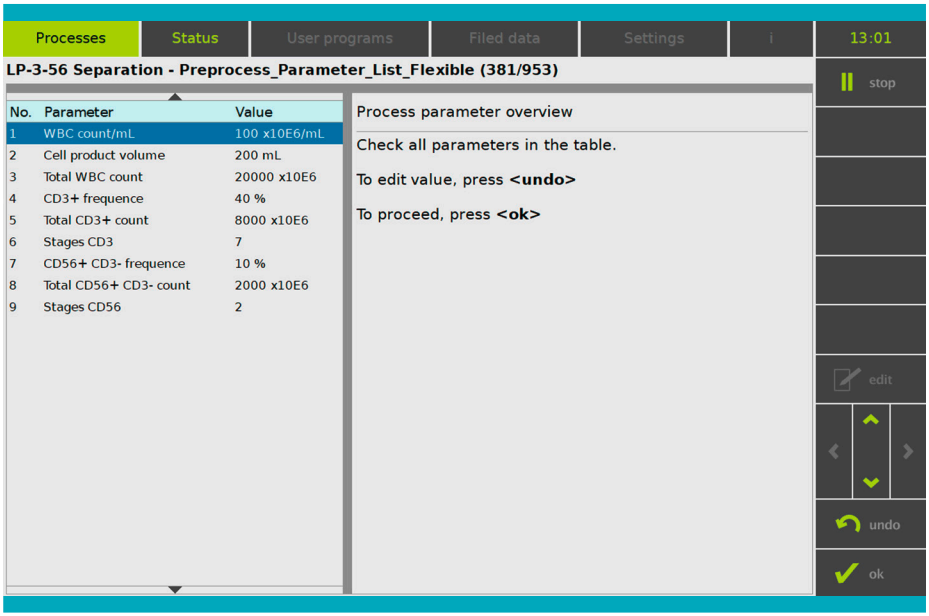
Screen 7.38: Entry of cell frequency of CD3-positive cells



Screen 7.39: Entry of cell frequency of CD3-negative and CD56-positive cells



Screen 7.40: Entry of volume of starting cell product



Screen 7.41: Verification of entered values

Tap <undo> to control and revise the list of parameters. For the revision, the process will return to Screen 7.37 (see section 7.5.1 ´Parameter input´).

7.5.2 Transfer of CliniMACS Reagents and IgG solution

The CliniMACS Reagents need to be transferred into the respective bag on the tubing set. The figure below shows the following preparative steps that need to be performed:

Figure 7.9 shows how to transfer the CliniMACS Reagents into the bag.

1. Remove the plastic caps of the reagent vial. Remove the contents of the vial using a suitable Luer Lock syringe equipped with a needle. Carefully remove the needle from the syringe (see Figure 7.9, part 1).
2. Connect the syringe via Luer Lock connection to the respective reagent bag of the tubing set. Initially, evacuate the air from the bag (see Figure 7.9, part 2).
3. Turn around bag and syringe and transfer the reagent (without air) in one go through the sterile filter into the bag (see Figure 7.9, part 3). Remove the syringe. Hang the reagent bag on the hook on the respective bag hanger. Ensure that the liquid can flow freely.

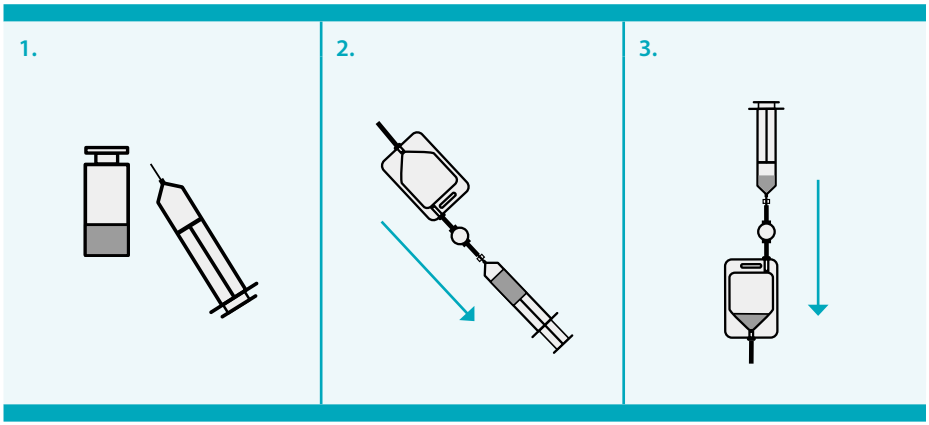


Figure 7.9: Transfer of reagent into the reagent bag of the tubing set

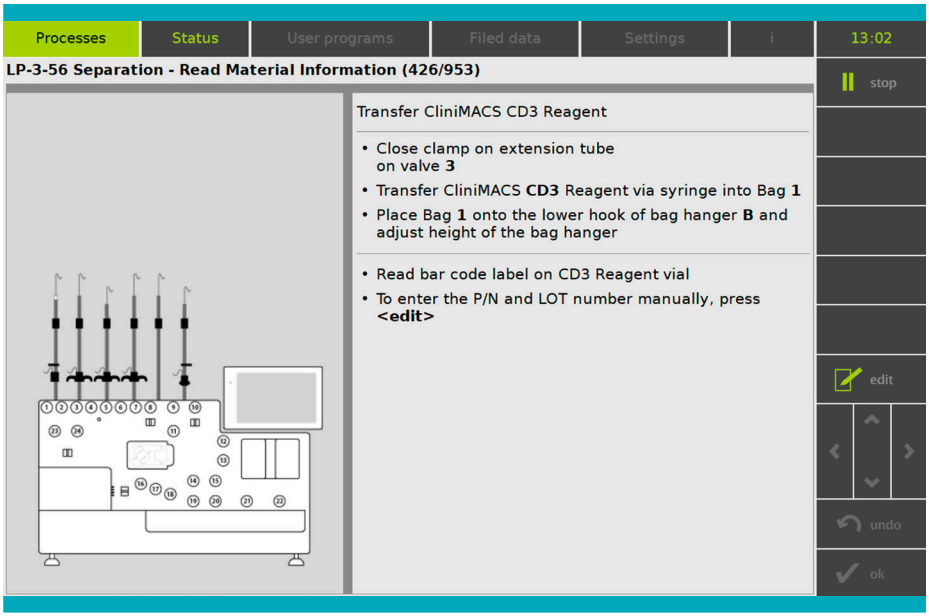
An overview of all bags for the different reagents and their location is described in Table 7.2.

IMPORTANT

Close the clamps on Bag 3 and Bag 5 as well as on the extension tube at valve 3.

Reagent	Bag no.	Bag hanger
CliniMACS CD3 Reagent	1	B
CliniMACS CD56 Reagent	2	C
IgG solution	4	D

Table 7.2: Overview of Reagent Bag set-up



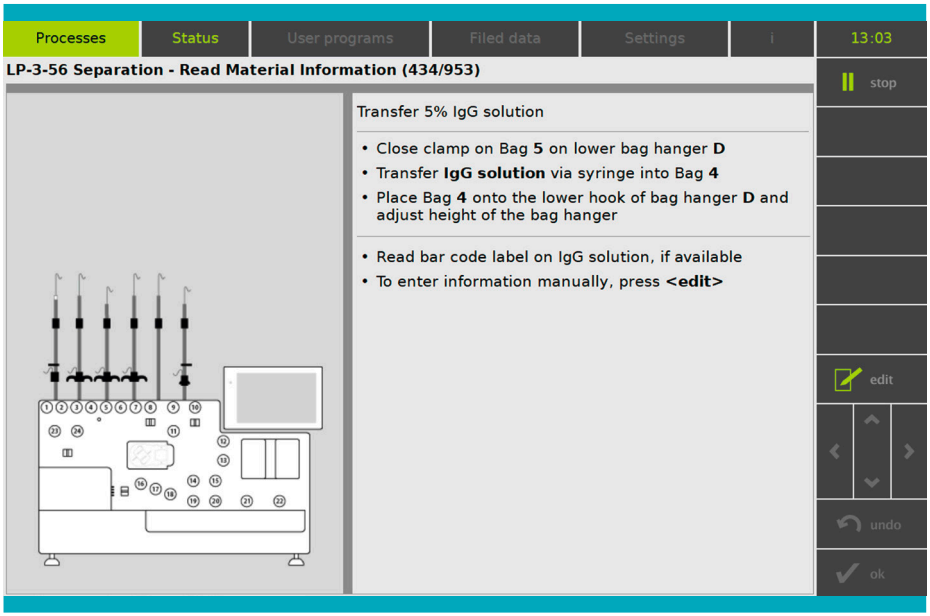
Screen 7.42: Transfer of CliniMACS CD3 Reagent

Read the barcode label on the reagent vial or tap <edit> to enter information manually with the keyboard shown on the screen.

Transfer one vial of CliniMACS CD3 Reagent to Bag 1 on valve 3. For transfer and connection, refer to Figure 7.9.

IMPORTANT

Ensure that the clamp on the extension tube is closed and that the clamp on Bag 1 at valve 3 is open.



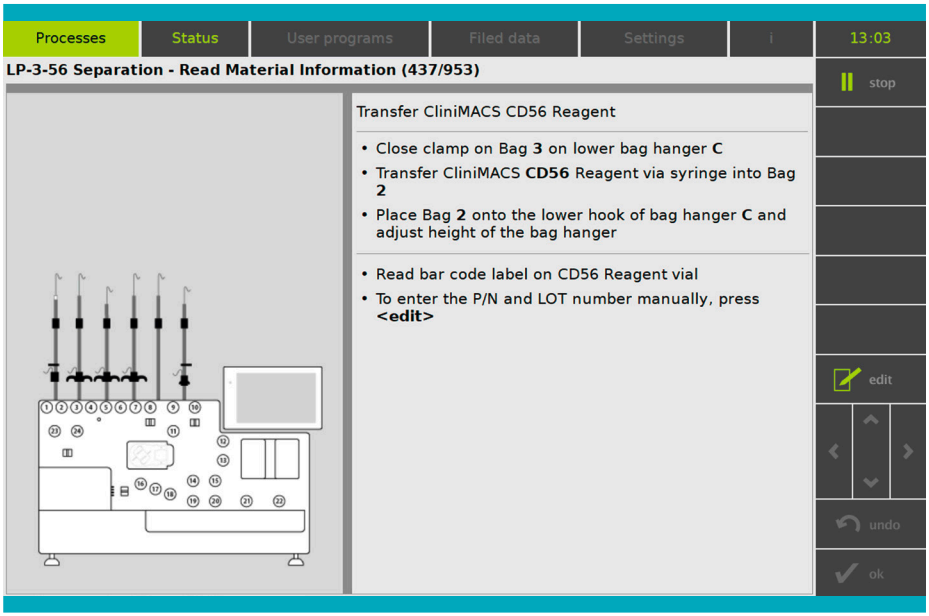
Screen 7.43: Transfer of IgG Solution

Read the barcode label of the IgG solution or tap <edit> to enter information manually with the keyboard shown on the screen.

Transfer 10 mL of 5% IgG solution to Bag 4 on valve 6. For transfer and connection, refer to Figure 7.9.

IMPORTANT

Ensure that the clamp on Bag 5 is closed and that the clamp on Bag 4 on valve 6 is open.



Screen 7.44: Transfer of CliniMACS CD56 Reagent

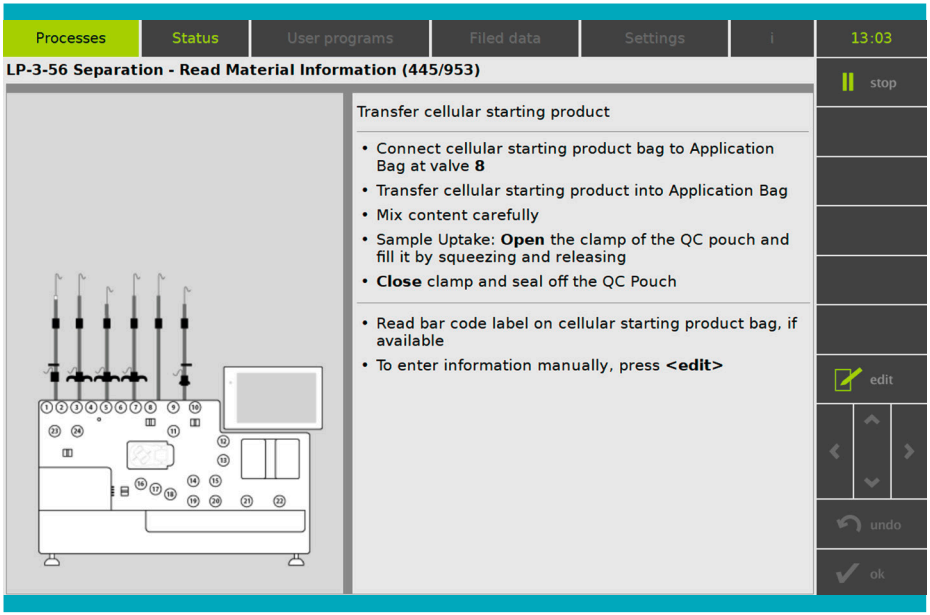
Read the barcode label on the reagent vial or tap <edit> to enter part numbers (P/N) and LOT numbers manually with the keyboard shown on the screen.

Transfer one vial of CliniMACS CD56 Reagent to Bag 2 on valve 4. For transfer and connection, refer to Figure 7.9.

IMPORTANT

Ensure that the clamp on Bag 3 is closed and that the clamp on Bag 2 on valve 4 is open.

7.5.3 Transfer of the starting cell product



Screen 7.45: Transfer starting cell product to Application Bag

For the transfer of the starting cell product into the Application Bag, follow the institution's standard operation procedures. For example, connect the container using either a sterile tubing connection, a Luer Lock connection, or a spike port connection. Transfer the starting cell product into the Application Bag and seal off the empty bag.

Use the QC Pouch to take a sample from the Application Bag. After the cell product has been transferred and mixed properly:

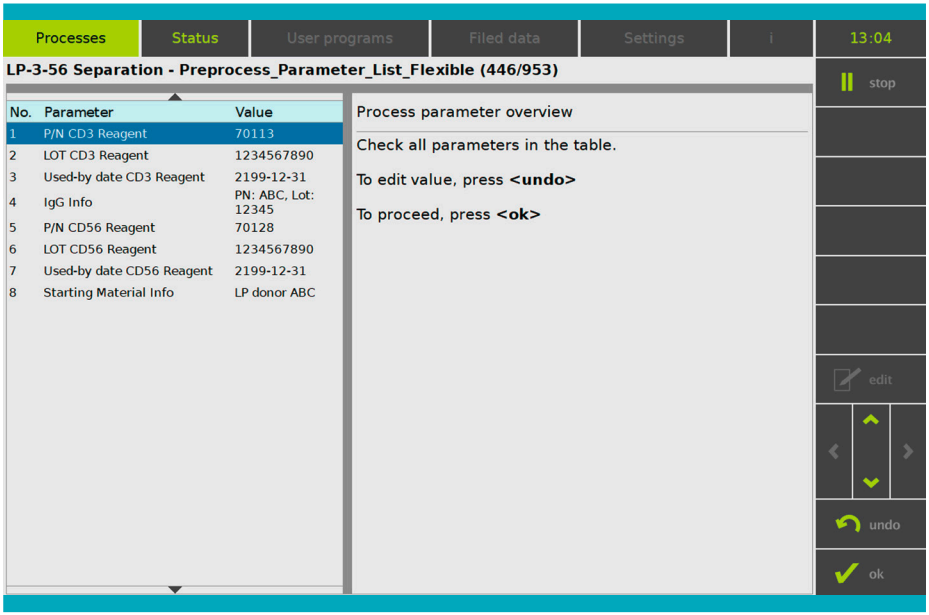
1. Open the QC Pouch clamp.
2. Squeeze and release the pouch once to transfer a representative sample into the pouch. Multiple squeezes and releases will increase the sample volume in the QC Pouch. The maximum volume of the QC Pouch is 4 mL.
3. Close the clamp and seal off the pouch.

The QC sample should be analyzed following the institution's standard operating procedures.

Tap <edit> to manually enter further information with the keyboard.

IMPORTANT
After the transfer of the starting cell product into the Application Bag and before the entire process starts, a sample can be taken from the starting cell product. For further analysis, a sample can be taken from the Target Cell Bag as well.

7.5.4 Final process set-up



Screen 7.46: Final setup check for process

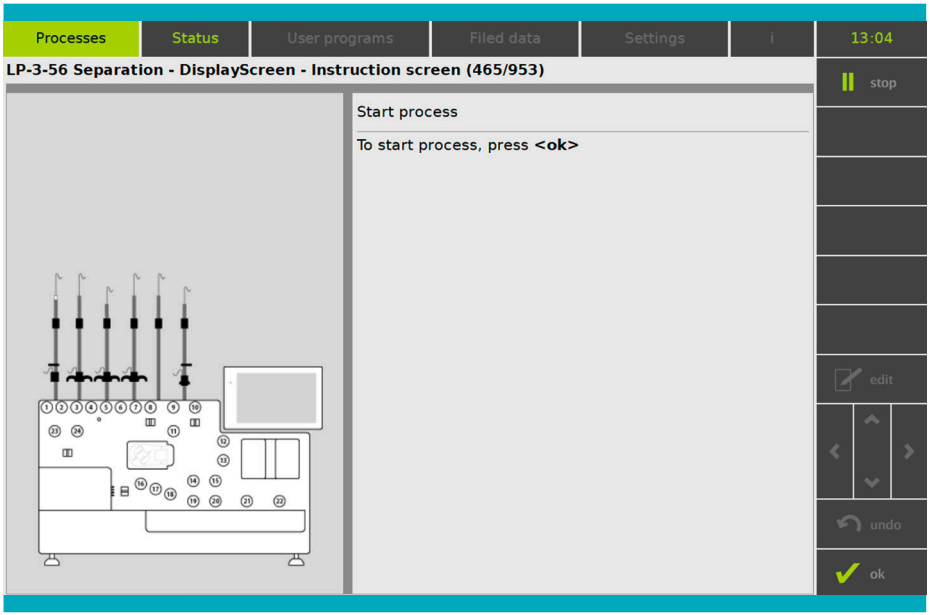
Tap <undo> to control and revise the list of parameters. For the revision, the process will return to Screen 7.42 (see section 7.5.2 ´Transfer of CliniMACS Reagents and IgG solution´).

Note: At this time, all preparative steps are completed and the automated separation process can be started.

7.6 Automated separation process

7.6.1 Start of separation process

To start the CD3 depletion and CD56 enrichment process, tap <ok> as described in Screen 7.47.



Screen 7.47: Start of the automated separation process

IMPORTANT

Ensure that the required starting cell product is loaded into the CentriCult Unit.

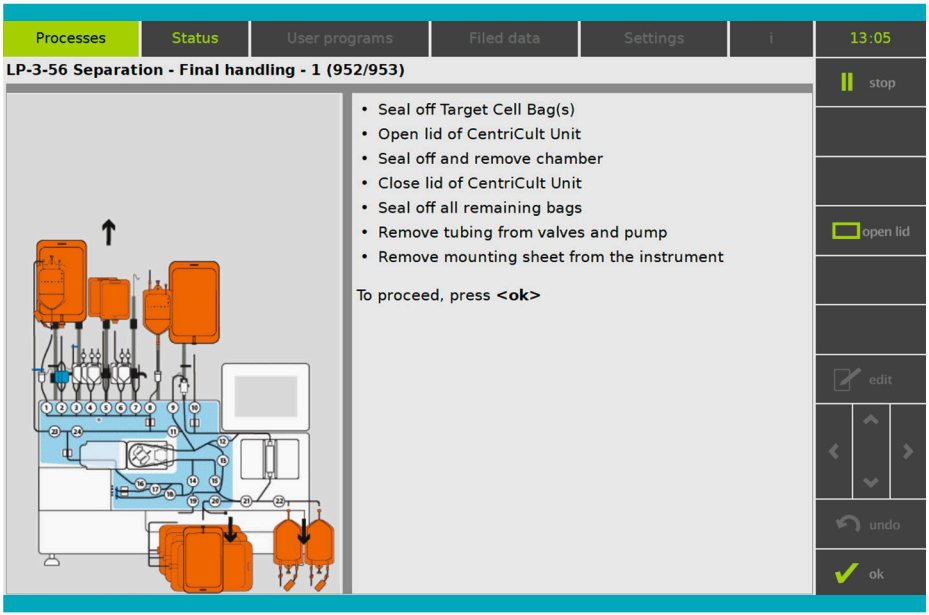
7.6.2 Completion of separation process

⚠ CAUTION

Risk of reduced quality of target cells. Other solutions for the resuspension of the final cell product than those specified in chapter 4 ´Materials required´, can lead to reduced quality of the target cells.

- Ensure that the target cells are resuspended in formulation solution (except for use case 2).

For additional safety, check the remaining level in the formulation solution bag after process completion to see if the required volume has been used up.

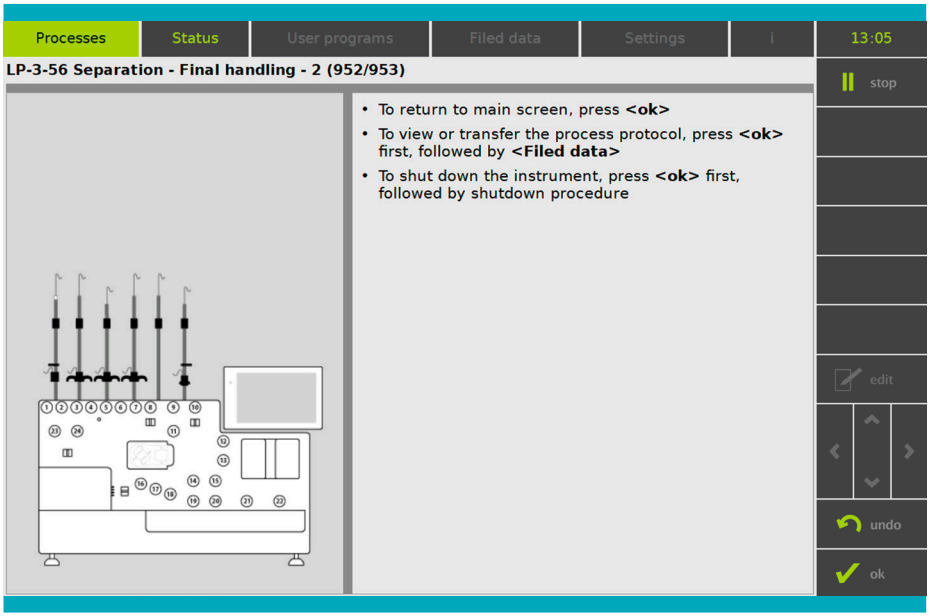


Screen 7.48: Final handling after the separation process is completed

After completion of the entire process, seal off the Target Cell Bag 1 and Non-Target Cell Bag. Take a sample from the Target Cell Bag 1 and optionally from the Non-Target Cell Bag for further analysis. Store the samples at +4 to +8 °C (+36 to +46 °F).

The CentriCult Unit lid unlocks automatically during this process step. If the lid does not unlock automatically, tap <open lid> on the tool bar. In case the lid cannot be opened, contact Miltenyi Biotec Technical Support.

Note: Discard the tubing set as biohazardous material according to the institutional's standard operating procedures.



Screen 7.49: Completion of process

The process log file is saved and stored in <Filed data> and can be transferred to other media with a standard USB storage device. To do so, plug the USB storage device into the USB port located on the side of the touchscreen. Tap <Filed data> on the menu bar and select the requested process. Then tap <save> to transfer the process protocol to the USB storage device.

7.6.3 Shutdown and switch off the instrument

Always perform a shutdown procedure before switching off the instrument. In the <Settings> menu, select the program <Shutdown> in the <Tools> group and tap <run>. Once the shutdown is completed, the instrument can be switched off safely.

7.6.4 Cleaning and disinfection

⚠ CAUTION

Risk of cell damage by UV radiation. Exposure to UV radiation can lead to damage of cells.

- Do not use UV radiation for disinfection during the process.

The instrument should be cleaned and disinfected after each procedure. Refer to the CliniMACS Prodigy user manual (instrument) regarding the cleaning and disinfection of the instrument. It is recommended to follow the standard operating procedures for the treatment of potentially infectious materials.

7.6.5 Analysis of cells

⚠ CAUTION

Risk of reduced quality of target cells. The target cells must be analyzed and confirmed to meet user requirements, otherwise the suitability for clinical application can be compromised.

- Examine the target cells regarding quality and quantity according to their intended use.

Do not store samples in the QC Pouches. QC samples should be stored in suitable containers at +4 to +8 °C (+39 to +46 °F) or according to institutional guidelines. All QC samples should be analyzed according to standard operating procedures. Contact Miltenyi Biotec Technical Support for assistance, if required.

Note: Determine the total volume in the Target Cell Bag 1 to calculate the total number of target cells. If required, determine the volume in the other fractions (e.g., Non-Target Cell Bag) as well.

IMPORTANT

The Target Cell Bags included in the tubing set are not intended for storage or transport of cells for more than 24h. If the target cells are not used for direct application, special attention should be paid to preserve stability and functionality of the target cells in elution solution and the storage container used.

For the manufacture and use of the target cell product, national and international legislation and regulations must be followed. Miltenyi Biotec as the provider of the CliniMACS Prodigy LP-3-56 System does not provide any recommendations regarding the use of the manufactured cells for therapeutic purposes and does not make any claim regarding a clinical benefit.

8 Troubleshooting

In any case of instrument malfunction or process failure, contact the Miltenyi Biotec Technical Support at:

+49 2204 8306-3803
technicalsupport@miltenyi.com

Visit www.miltenyibiotec.com for local Miltenyi Biotec Technical Support contact information.

9 Legal notes

8.1 Limited warranty

Except as stated in a specific warranty statement, which may accompany this Miltenyi Biotec product, or unless otherwise agreed in writing by a duly authorized Miltenyi Biotec representative, Miltenyi Biotec's warranty for products purchased directly from Miltenyi Biotec shall be subject to the terms and conditions of sale under which it was provided to you by the respective Miltenyi Biotec sales organization. These terms and conditions are available on request or at www.miltenyibiotec.com. The applicable terms and conditions of sale may vary by country and region. Nothing herein should be construed as constituting an additional warranty.

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To determine the warranty that came with your product, see your packing slip, invoice, receipt or other sales documentation. Some components of a product combination you purchased may have a shorter warranty than that listed on your packing slip, invoice, receipt or other sales documentation (e.g., goods subject to shelf life and obsolescence).

Miltenyi Biotec's warranty for this product only covers product issues caused by defects in material or workmanship during normal use. It does not cover product issues caused by any other reason, including but not limited to product issues due to use of the product in a manner other than specifically described in this manual, for example: inappropriate or improper use; incorrect assembly or installation by an operator or a third party; reasonable wear and tear; negligent or incorrect operation, handling, storage, servicing, or maintenance; non-adherence to the operating instructions; unauthorized modification of or to any part of this product; or use of inappropriate consumables, accessories, or work materials.

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Miltenyi Biotec must be informed immediately, if a claim is made under such warranty. If a material or manufacturing defect occurs within the warranty period, Miltenyi Biotec will take the appropriate steps to restore the full usability of the instrument.

Limitation on damages
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