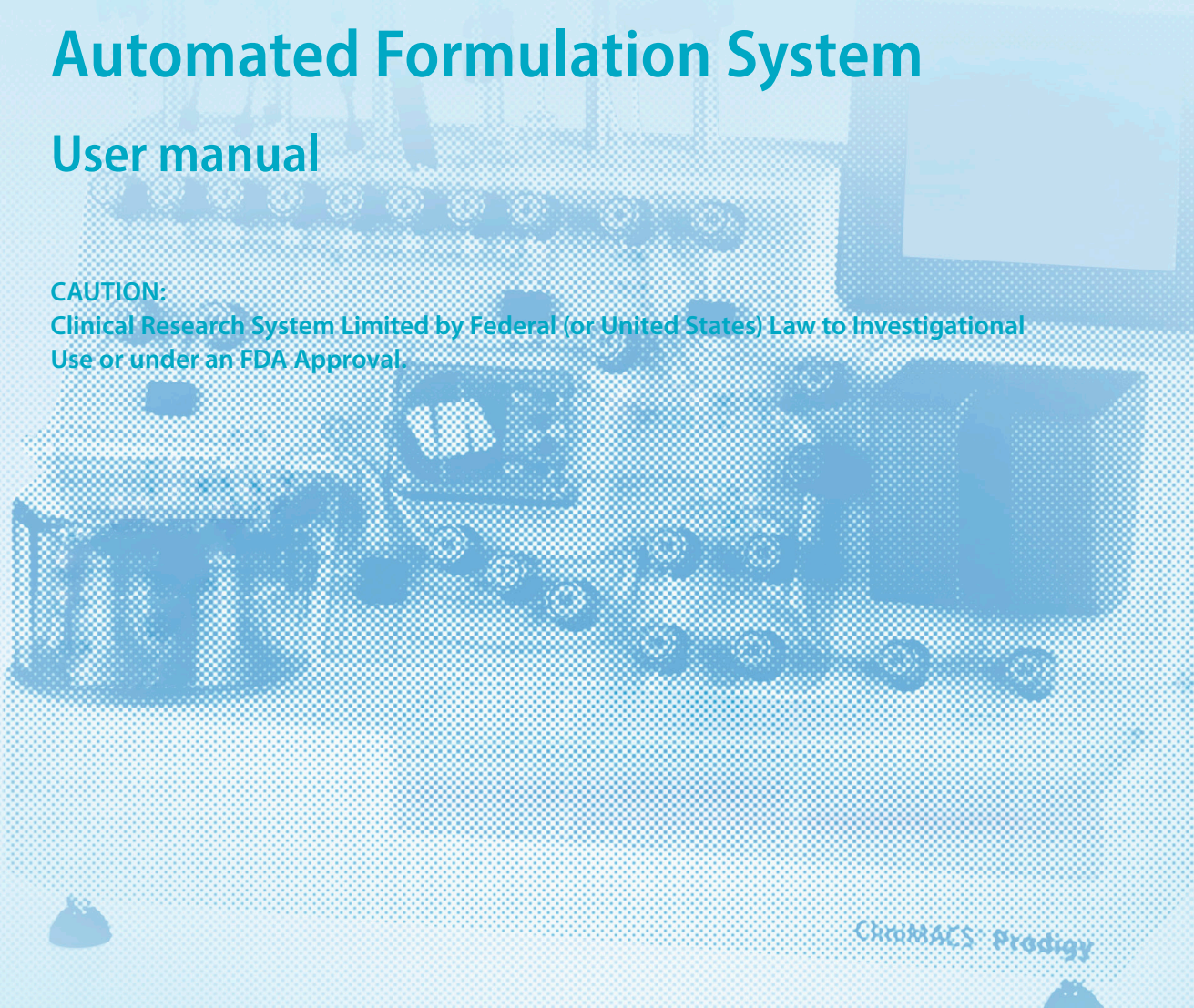
Miltenyi Biotec

CliniMACS Prodigy®
T Cell Transduction and Automated Formulation System

User manual

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®
T Cell Transduction and Automated Formulation System

User manual

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1

About this user manual

This user manual provides information for the use of the CliniMACS Prodigy T Cell Transduction and Automated Formulation 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 cell product are described in the CliniMACS Prodigy user manual (Instrument). For instructions for use for example, warnings and precautions, concerning the CliniMACS Prodigy T Cell Transduction and Automated Formulation System components, refer to the instructions for use provided for the respective component.

1.1 Essential information

⚠ WARNING

Risk of electrical shock, physical injuries, instrument damage or malfunction.

Disregard of any instructions, warnings or cautions at any time can endanger, users and others and may compromise the electrical, electronical, electromagnetic and mechanical safety. Disregard also excludes the manufacturer from any liability.

- The operation of the instrument must be performed by trained operators only.
- Before using the instrument, carefully read and understand the safety information, warnings, precautions, and instructions for proper operation provided in this user manual including without limitation the safety information in section 5.2 ´General safety instructions´ 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.
- Adhere to all safety information, warnings, precautions, and instructions at all times while the instrument is in operation.
- Retain the user manuals 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.

1.2 Associated documents

This user manual is part of a series and should only be used in conjunction with the other user manuals of the series.

- CliniMACS Prodigy Instrument user manual
- CliniMACS Prodigy Software user manual

1.3 Presentational conventions

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

1.4 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
Bold <colored> text	Indicates software elements, for example, a button or a tab of the user interface
See section 1.4 ‘Text styles’	References to the section with the number 1.4 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.

1.4.1 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.

1.4.2 Warning messages

The color and signal word of a warning message depend on the hazard level (see section 5.1 ‘Hazard levels’). 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

T cells can be stably modified by introduction of genetic material using viral vectors. For example, T cells can be genetically modified to express T cell receptors (TCRs), or chimeric antigen receptors (CARs) which redirect them to specific targeting and killing of tumor cells for improved clinical outcome of adoptive T cell therapy approaches.

The generation of genetically modified T cell product requires sequential steps:

- Cell separation
- T cell activation
- Transduction
- Expansion
- Formulation and filling

The CliniMACS Prodigy T Cell Transduction and Automated Formulation System allows the entire process starting from fresh or frozen leukapheresis, whole blood cells or peripheral blood mononuclear cells (PBMCs), including formulation and filling of the cell product to be performed in an automated and closed system (see Figure 3.1). Samples for quality control can also be obtained during manufacturing using sterile techniques.

The T Cell Transduction and Automated Formulation System was especially designed for the manufacturing of genetically modified T cell products in an end-to-end process including formulation and filling.

The components which are required to perform the CliniMACS Prodigy T Cell Transduction and Automated Formulation are described in chapter 4 ´Materials required´ on page 19 of this user manual.

This user manual provides guidance for the use of the CliniMACS Prodigy T Cell Transduction and Automated Formulation in order to manufacture genetically modified T cells for clinical application.

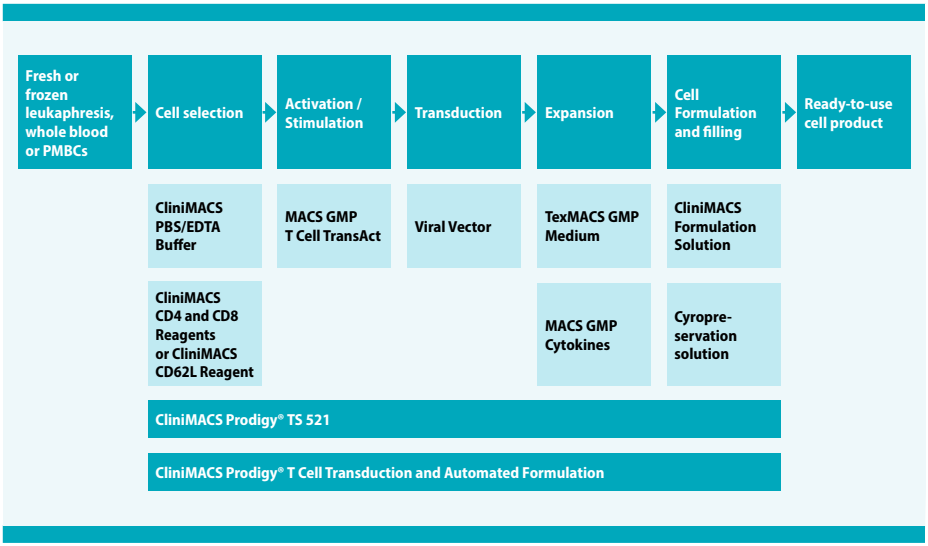


Figure 3.1: Generic manufacturing scheme using the CliniMACS Prodigy T Cell Transduction and Automated Formulation

IMPORTANT

This user manual describes the full process and includes a recommended protocol. To ensure a high-quality cell product, Miltenyi Biotec recommends using the cytokines and media stated in this user manual.

3.2 Process

In summary, the full process (case 1) of the T Cell Transduction and Automated Formulation process guides through all steps of the process, starting with the installation of the CliniMACS Prodigy TS 521 on the CliniMACS Prodigy.

Once the tubing set installation is complete, the following materials are supposed to be connected to the CliniMACS Prodigy:

- CliniMACS PBS/EDTA Buffer supplemented with human serum albumin (HSA)
- TexMACS™ GMP Medium supplemented with MACS® GMP Cytokines and human AB serum (optional)

The CliniMACS Prodigy TS 521 is then primed before the blood product is connected to the tubing set.

Once the CliniMACS Reagents are connected, the blood product is connected to the tubing set. Afterwards, the cell enrichment takes place. Initial washing, cell labeling and magnetic separation are automatically performed.

Enriched cells will be directed to a dedicated bag from which a sample can be taken for analysis. After providing the required input, the necessary number of enriched cells is seeded in the cultivation chamber where all subsequent phases of cell cultivation take place.

The user is asked to enter the cultivation parameters: CO_2 concentration and temperature. Furthermore, the software requests to plan the cultivation using an activity matrix that enables T cell stimulation with a stimulation reagent e.g., MACS GMP T Cell TransAct™. Cultivation includes but is not limited and also not obliged to the following activities: stimulation, transduction (viral vector), culture wash, medium exchange, chamber shaking, formulation and filling.

The resulting product is then ready for clinical application or further processing (e.g., further culture, enrichment, cryopreservation, or functional testing).

Activities will be executed according to the activity matrix defined by the user, which can be saved and loaded, as well as edited during the cultivation period.

Culture monitoring and quality control can be performed with the available microscope and sampling functions. The status of the aforementioned steps can be monitored on the screen of the CliniMACS Prodigy. The few manual handling steps are guided by the graphic user interface and this user manual.

Case 1: Full process
Choose this option to run the complete process. This includes tubing set installation, tubing set priming, T cell enrichment, setup of T cell culture, stimulation, transduction, expansion and formulation and filling of cells as described above.

Case 2: T cell cultivation
Choose this option if only the setup of T cell culture, stimulation, transduction, expansion and formulation and filling should be performed. No T cell enrichment is performed. A tubing set must already be installed.

Case 3: T cell cultivation with tubing set installation
Use this option to perform a manufacturing run without T cell enrichment and when the tubing set has not yet been installed. The tubing set is primed with medium in this case.

Case 4: Resume cases
Use this option if the T cell cultivation phase was interrupted during cultivation or harvest and needs to be resumed. Depending on the situation, different resume subcases can be chosen.

⚠ CAUTION

Risk of low performance or loss of the cell product. If the process is interrupted there is the risk of low performance or loss of the cell product.

- Choose "Resume cases" to continue the cell cultivation process.

Case 4.1 Resume T Cell cultivation
This function starts directly with the culture. Enter the adjustment factor and CO_2 concentration. Then set up the activity matrix and enter the current culture volume. Be aware that entries in the activity matrix and logfile protocol entries are not saved on the device after an unexpected shutdown. When case 4.1 is executed the user must start with a new activity matrix and the current day refers to day 0.

Case 4.2 Resume harvest
This resume function starts directly with the selection of one of the five end of culture types.

Case 4.3 Resume formulation
The function skips the rebuffering of cells in formulation solution and starts directly with the formulation and filling of a fresh or frozen cell product.

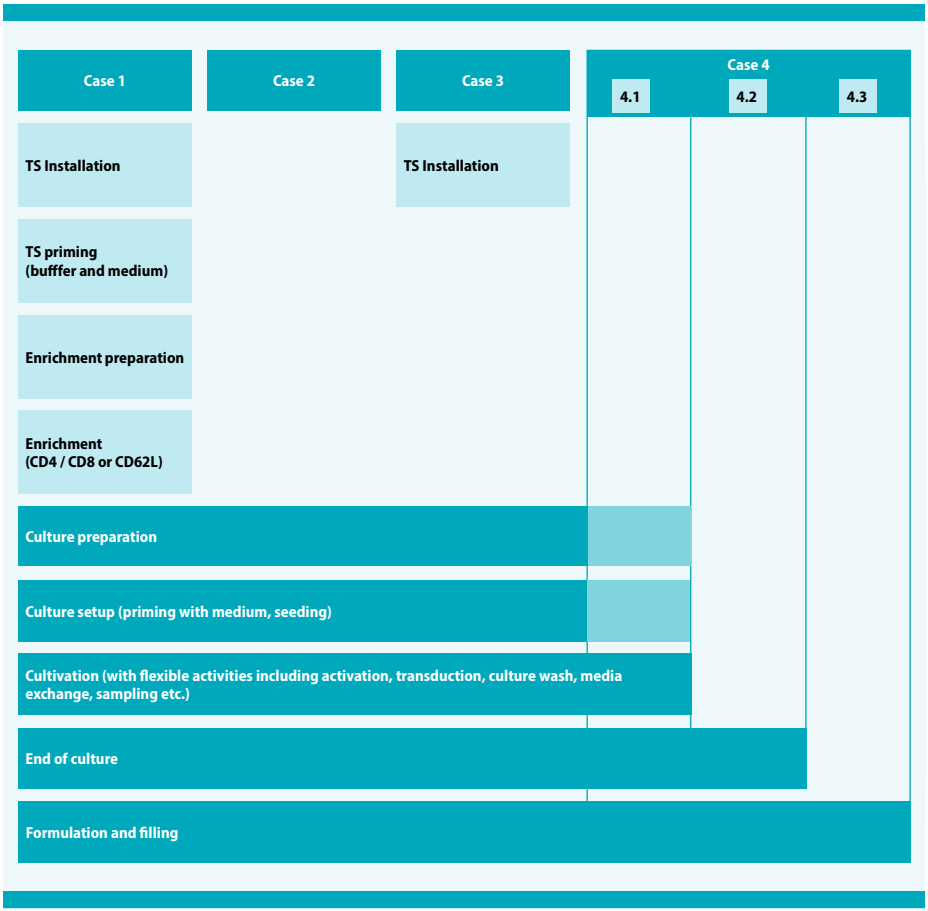


Figure 3.2: Versatility of the T Cell Transduction and Automated Formulation process

IMPORTANT

The process has a maximum capacity with respect to cell enrichment and cell transduction. Details are described in chapter 6 ´Preparative steps´ on page 25.

4

Materials required

The following section outlines the materials and consumables required for the generation of genetically modified T cells with the CliniMACS Prodigy T Cell Transduction and Automated Formulation System.

4.1 CliniMACS Prodigy T Cell Transduction and Automated Formulation System components

The following components are required for the process (see Table 4.1):

Material	Quantity	Required for case(s)	Comment
CliniMACS Materials			
CliniMACS Prodigy	1	All[1]	
CliniMACS Formulation Unit	1	All[1]	
CliniMACS CD62L Reagent	1 vial	1	For CD62L enrichment only
CliniMACS CD4 Reagent	1 vial	1	In combination with CD8 enrichment
CliniMACS CD8 Reagent	1 vial	1	In combination with CD4 enrichment
CliniMACS Prodigy TS 521	1 set	All[1]	
CliniMACS PBS/EDTA Buffer	3 L	1	Use 1 × 3 000 mL bag (in case of 3 stages of enrichment 2 ×3000 mL bags)
MACS GMP Materials			
TexMACS GMP Medium	6 L	All[1]	3 bags
MACS GMP Recombinant Human IL-7	3 vials 25 µg/vial	All[1]	In combination with IL-15

Material	Quantity	Required for case(s)	Comment
MACS GMP Recombinant Human IL-15	3 vials 25 µg/vial	All[1]	In combination with IL-7
MACS GMP Recombinant Human IL-2	3 vials 25 µg/vial	All[1]	If IL-2 is used for T cell expansion
MACS GMP T Cell TransAct	1 vial	1, 2, 3, optional in case 4.1[1]	
MACS GMP Vectofusin®-1	1 vial	Optional, for transduction e.g., with retroviral vectors	Will be pre-mixed with viral vector
Software			
T Cell Transduction and Automated Formulation (TCTf - process version)			

1 **Note**: For all the resume cases (case 4 with potential subcases), be aware that the required materials have been prepared/connected during the original run and can be further used for the resume cases. Depending on the time for the process to be resumed, material not yet provided will then be required for the resume cases.

Table 4.1: Materials required for the CliniMACS Prodigy T Cell Transduction and Automated Formulation System

IMPORTANT

The materials referenced above are recommended for the use in the T Cell Transduction and Automated Formulation. The use of CliniMACS GMP Reagent is recommended for cell selection. Amounts will differ if the protocol is modified. The user is responsible for the validation of the process.

4.2 Additional materials required

Besides the CliniMACS Prodigy T Cell Transduction and Automated Formulation System components, additional materials are required (see Table 4.2).

Material	Comment
Biological materials	
Heterogeneous hematologic cell sources	Not older than 24 hours (fresh) $<2 \times 10^{10}$ white blood cells (WBCs)
• Fresh leukapheresis • Frozen leukapheresis • Whole blood • Peripheral blood mononuclear cells	50–300 mL 50–300 mL 50–300 mL 50–300 mL
Human serum albumin (HSA)	Use only pharmaceutical grade HSA approved in your country.
Material	**Comment**
Human AB serum	Use only GMP grade product.
Sterile water	Pharmaceutical grade
Viral vector	Lentiviral or gamma-retroviral vector in a bag
Formulation solution	2 L, e.g., CliniMACS Formulation Solution
Cryopreservation solution	e.g., CliniMACS Cryo Supplement, 450 mL
Consumables	
Syringes	• 5 mL, several • 10 mL, several • 50 mL, several
Hypodermic needles	20 gauge, several
Transfer bag, 150 mL	1 bag
Luer/Spike Interconnector	1 piece
Equipment	
Uninterruptable power supply	
CO_2 and compressed air supply	
Sterile tubing welder, e.g., Terumo Sterile Connecting Device	

Table 4.2: Additional materials required for the CliniMACS Prodigy T Cell Transduction and Automated Formulation

IMPORTANT

This protocol requires the use of components and materials which are not part of the CliniMACS Prodigy T Cell Transduction and Automated Formulation System, e.g., human serum albumin or human AB serum. Only use pharmaceutical-grade HSA approved in your country and GMP-grade human AB serum. If not available as registered drugs, all risks arising from these components must be evaluated before application of the target cell product to humans.

5

Warnings and precautions

5.1 Hazard levels

The following chart depicts the symbols used in this user manual to inform the user about potential risks if the outlined warnings and precautions are not followed. Icons on the left side specify the risk. The hazard level classifies the hazard, as described below. The level, type, and source of the hazard, as well as potential consequences, prohibitions, and measures are indicated as follows.

⚠ WARNING

Indicates a hazardous situation which, if not avoided, could result in death or serious injury.

- Measures to avoid the hazard.

⚠ CAUTION

Indicates a hazardous situation which, if not avoided, could result in minor or moderate injury.

- Measures to avoid the hazard.

NOTICE

Indicates information considered important, but not hazard-related (e.g., messages relating to property damage).

- Measures to avoid the hazard.

IMPORTANT
Is used to advise the user of important practices or information not related to personal.

5.2 General safety instructions

This section explains the potential risks associated with the operation of the CliniMACS Prodigy T Cell Transduction and Automated Formulation System.

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 cellular starting product are described in the CliniMACS Prodigy user manual (Instrument).

For instructions for use, e.g., warnings and precautions, concerning the CliniMACS Prodigy T Cell Transduction and Automated Formulation System components, refer to the instructions for use provided for the respective component.

6

Preparative steps

⚠ WARNING

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

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

The process requires a few preparative steps.

6.1 Testing of cell product

The process contains an enrichment process, which is a multi-stage loading program that can process more cells than the single column capacity would allow. This means that the cell concentration of WBCs and the frequency of labeled cells must be determined before the enrichment in order to calculate the appropriate number of stages. A maximum of three stages of 1×10^9 labeled cells each can be processed.

Therefore, analyze the cell product prior to connecting it to the tubing set. Determine the WBC concentration and the frequency of cells to be labeled (either CD4 and CD8 positive among viable CD45 positive cells or CD62L positive among viable CD45 positive cells depending on the selected separation reagent).

IMPORTANT

If the cells are at a considerable low viability, it is recommended to consider the dead cells in the cell product to avoid an exceedance of the column capacity.

In order not to exceed the column capacity, start with a cell product volume containing a maximum of 2×10^{10} total WBCs and 3×10^9 cells to be labeled (i.e., CD4 and CD8 positive cells or CD62L positive cells, respectively). If using a frozen leukapheresis, parameters referring to the frozen cell product bag can be used.

The minimum volume of the cell product is 50 mL and the maximum volume is 300 mL for fresh or frozen cell product, respectively. For a frozen cell product an automatic dilution with medium or process buffer can be performed with a maximum total volume (including the volume of the cell product) of 300 mL. If the volume of the fresh cell product is below 50 mL, dilute the cell product with process buffer manually (see section 6.2 ´Preparation of process buffer´ on page 27).

The cell product parameters can be entered either at the beginning of the process or at the last possible time point directly before separation (e.g., if the analysis is performed while the cell labeling is running). It is recommended to determine the WBC concentration/volume/frequency before starting the process.

For further information see section 7.5.3 ´Prepare cell separation´ on page 71.

⚠ CAUTION

Risk of reduced quality of target cells. Wrong cell parameter input can lead to reduced quality of target cells. The cell parameter input must exactly reflect the actual values of the leukapheresis product to be processed.

- Ensure that no leukocyte population is excluded from the analysis.

6.2 Preparation of process buffer

Supplement 3 liters of CliniMACS PBS/EDTA Buffer with HSA to a final concentration of 0.5% (w/v), e.g., add 25 mL of 20% HSA per liter of buffer.

An additional buffer bag might be needed in case the process needs to perform three enrichment stages. The supplemented buffer is henceforth referred to as "process buffer".

IMPORTANT
This protocol requires the use of components and materials which are not part of the process, e.g., human serum albumin (HSA) or human AB serum. Only use pharmaceutical grade HSA approved in your country and GMP grade human AB serum. If not available as registered drugs, all risks arising from these components must be evaluated by the user before application of the target cell product to humans.

6.3 Preparation of medium

For optimal T cell proliferation, supplement 1 bag (= 2 L) of TexMACS GMP Medium with cytokines. For optimal results use IL-7 (MACS GMP Recombinant Human IL-7) in combination with IL-15 (MACS GMP Recombinant Human IL-15). Alternatively, IL-2 only (MACS GMP Recombinant Human IL-2) can be used.

Depending on the cell numbers used, varying cytokine concentrations and feeding schedule may be required. Titrate the cytokine concentration as needed.

The recommended dose ranges are:

- IL-7: 150–1,500 IU/mL (5–25ng/mL)
- IL-15: 85–450 IU/mL (5–25ng/mL)
- IL-2: 10–50 IU/mL

IMPORTANT
Optimal results were obtained when using 1 vial (25 µg) of MACS GMP Recombinant Human IL-7 and 1 vial (25 µg) of MACS GMP Recombinant Human IL-15 per 2 000 mL bag of TexMACS GMP Medium. Make sure the lot-specific activities comply with the recommended dose ranges.

For agitated T cell culture it is highly recommended to supplement the TexMACS GMP Medium with 3% human AB serum. The TexMACS GMP Medium (bag) is henceforth referred to as "medium bag".

IMPORTANT
Human AB serum is not a component of the CliniMACS Prodigy T Cell Transduction and Automated Formulation System. Use only GMP grade human AB serum.

It is possible to reduce the use of human AB serum by not supplementing further medium bags from day 5 or 6 until end of culture.

To prepare the medium bag:

- Reconstitute the lyophilized MACS GMP Cytokines using 1 mL of sterile water or medium.
- Add the appropriate amount of reconstituted cytokines to the medium bag using the Luer Lock port of the medium bag.
- Supplement both TexMACS GMP Medium bags with 60 mL (3%) human AB serum using the Luer Lock port of the medium bag.

If necessary, remove approximately 50 mL from the medium bag and store (e.g., in a transfer bag) at +4 to +8 °C (+39 to +46 °F) to use for dilution of the activation reagent and viral vector.

IMPORTANT
UV light could lead to adverse effects on the TexMACS GMP Medium. Protect the TexMACS GMP Medium from UV light using the provided protection bag (yellow).

7

Separation process

7.1 Initialization of the CliniMACS Prodigy

⚠ WARNING

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

- Connect all bags and vials by sterile welding.
- Perform all preparative steps in a sterile environment (e.g., laminar flow hood) using aseptic techniques.

Switch on the CliniMACS Prodigy with the ON/OFF switch located on the rear panel of the instrument.

⚠ CAUTION

Risk of delay in cell preparation. If the CliniMACS Formulation Unit is not connected to the CliniMACS Prodigy, the process will be canceled once a formulation valve is activated (e.g., for taking a sample).

- Make sure a CliniMACS Formulation Unit is installed on the instrument. Refer to the CliniMACS Prodigy Formulation Unit user manual for further instructions.

Parts of the text presented on the screens in the user manual may differ slightly from the screens shown on the instrument.

Use the touchscreen functionality and buttons on the menu and toolbar to operate the instrument. For details, refer to the CliniMACS Prodigy user manual (Instrument).

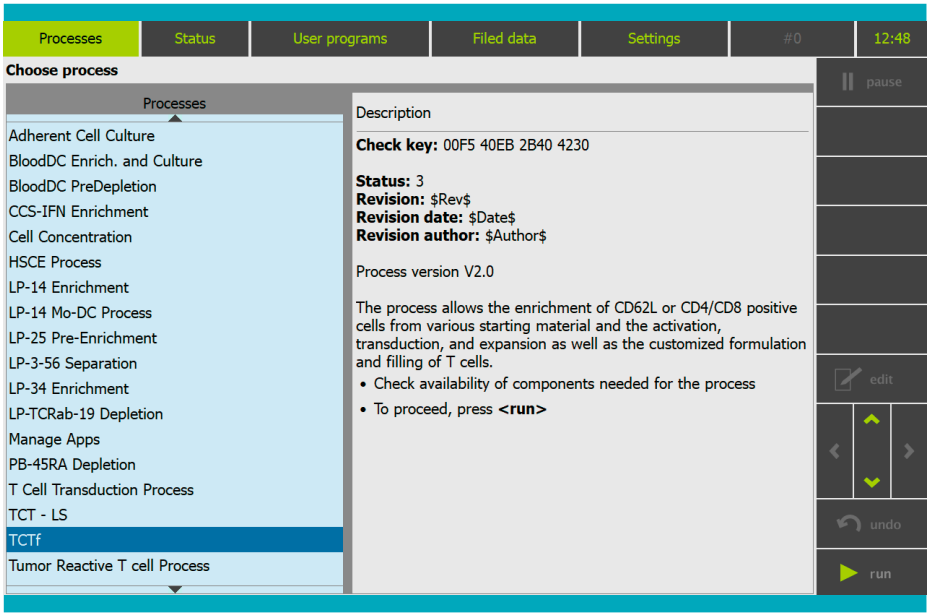
After the instrument initialization phase the main screen is shown. To start the T Cell Transduction and Automated Formulation process, select "TCTf" in the processes tab (see Screen 7.1). To confirm the selection, tap <run>.

Note: A user interface showing screens with instructions and pictures will guide through the entire procedure.

⚠ CAUTION

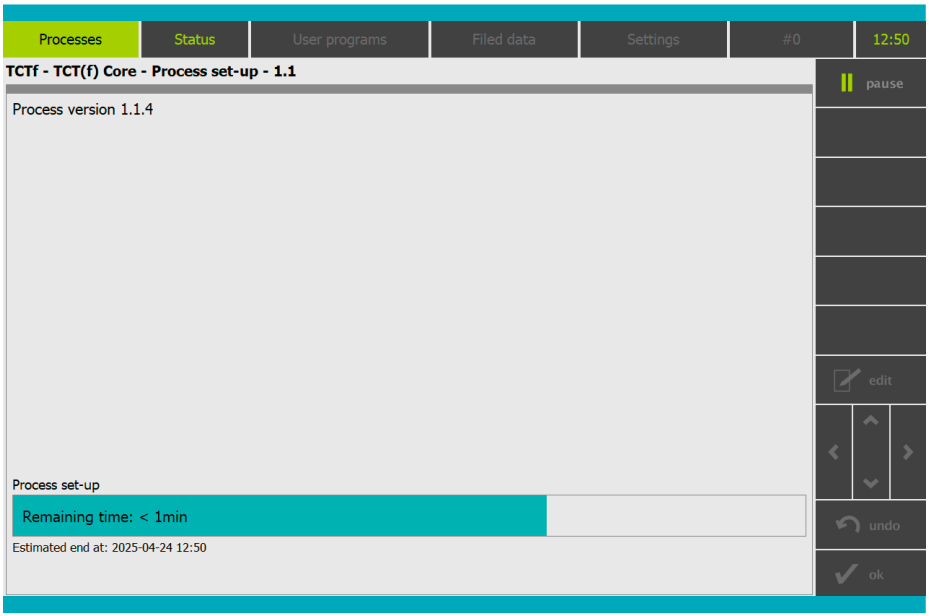
Risk of process failure. If alarm signals are not recognized and the required actions are not executed or confirmed there is the risk of process failure.

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



Screen 7.1: Choice of process TCTf

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



Screen 7.2: Self-test

7.2 Parameter input and process setup choice

⚠ CAUTION

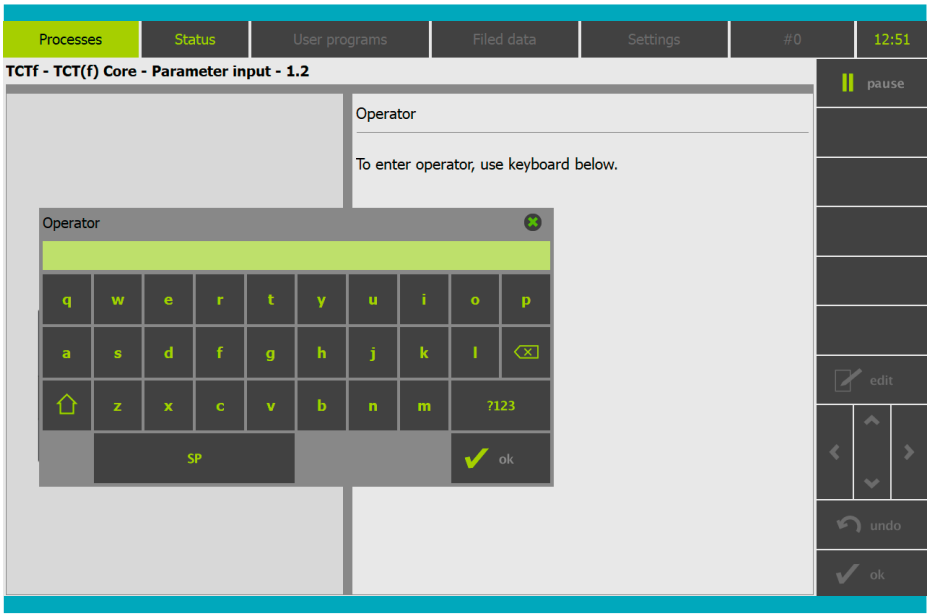
Risk of cell loss. Skipping the entry of parameters, such as frequency of labeled cells and cell product volume, can lead to process interruption if the allowed volumes are exceeded. The request for parameter entry will reappear directly before enrichment.

- It is not recommended to skip the entry of parameters.
- Do not exceed the allowed volumes. Ensure that the operator recognizes optical and acoustical alarm signals at any time during the process.

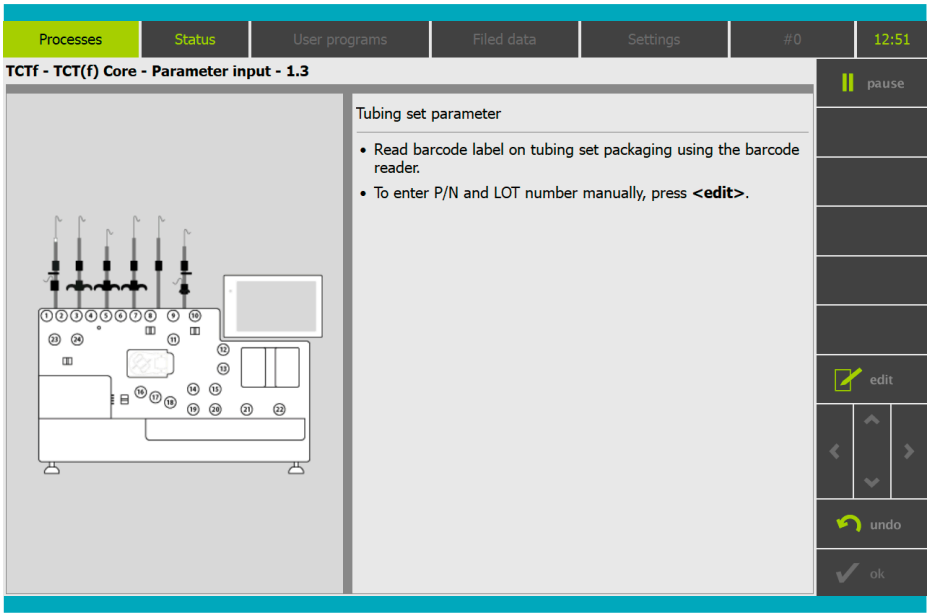
Multiple parameters must be entered for the process using either the barcode reader attached to the CliniMACS Prodigy or the keyboard shown on the screen. To confirm, tap <ok>. All entered parameters are saved in a process-related protocol.

Within the next steps of the process, enter information related to the user (see Figure 7.3) and CliniMACS Prodigy TS 521 (see Figure 7.1). For the manual entry of capital letters, tap <⇧>, for space tap <SP>, for numbers tap <?123>, and for

backspace tap <⌫>. If a user management system is active, no entry of operator-related information is required. Information on the logged-in user is saved automatically.

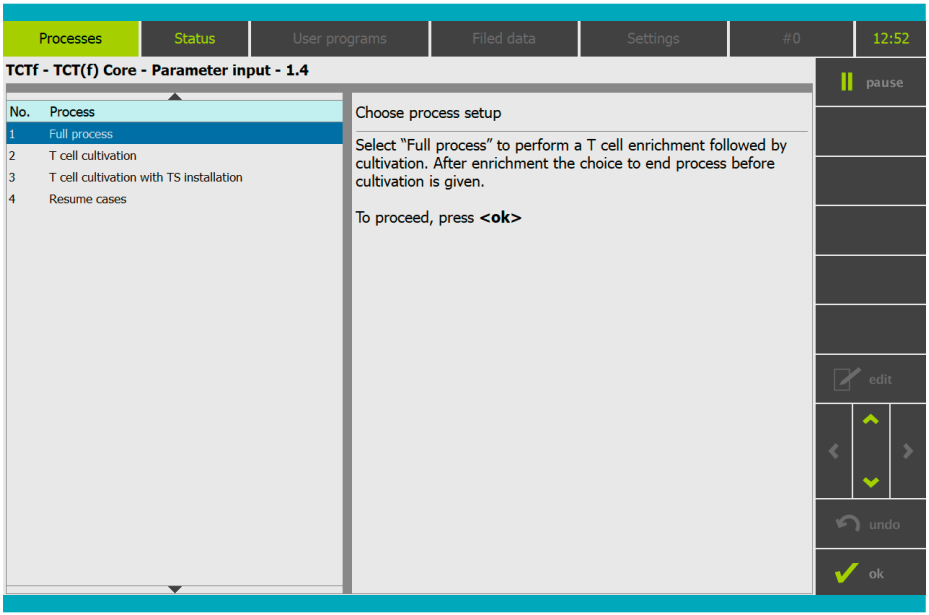


Screen 7.3: Entry of operator-related information



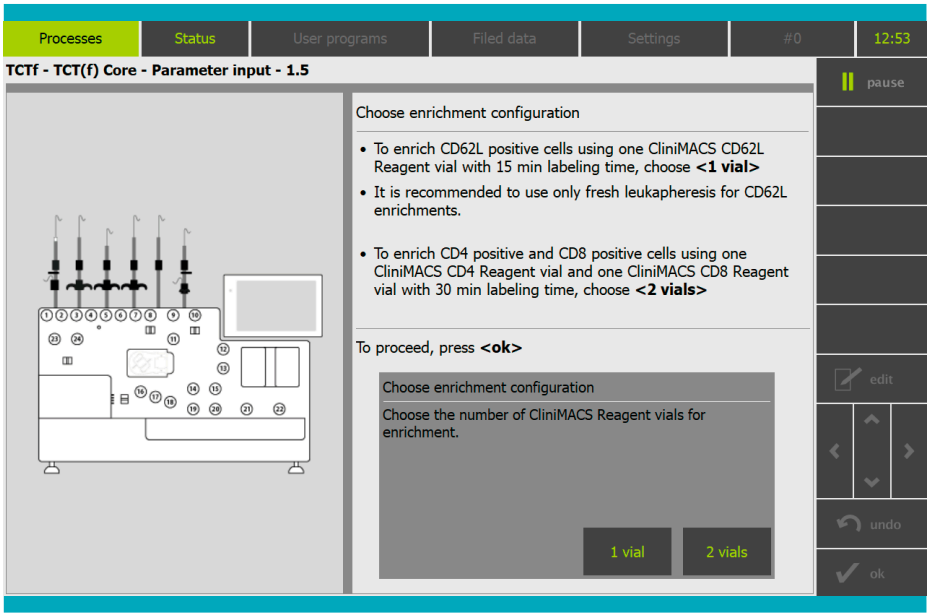
Screen 7.4: Entry of CliniMACS Prodigy TS 521 part number (P/N) and lot number (LOT)

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



Screen 7.5: Process setup no. 1 "Full process"

After parameter input, choose between four different cases (see section 3.2 ´Process´). Case 1, 2, and 3 have no subcases. Case 4 has three subcases (4.1 Resume T cell cultivation, 4.2 Resume harvest, and 4.3 Resume formulation). This user manual describes the complete process using case 1 (Full process) as the default process (see Screen 7.5).



Screen 7.6: Selection of enrichment configuration (1 or 2 vials)

In the next step, choose the number of vials of CliniMACS Reagent used for target cell enrichment. For CD62L enrichment, choose 1 vial, for a combined CD4 and CD8 enrichment, choose 2 vials (see Screen 7.6).

IMPORTANT

Use one vial of CliniMACS CD62L Reagent to enrich CD62L cells. The use of CliniMACS CD62L Reagent for frozen leukapheresis is not suitable due to the downregulation of the CD62L receptor. Use one vial of CliniMACS CD4 Reagent and one vial of CliniMACS CD8 Reagent to enrich CD4 and CD8 cells.

7.3 Tubing set installation

7.3.1 Components of the CliniMACS Prodigy TS 521

The components of the CliniMACS Prodigy TS 521 are pre-assembled and provided in a sealed and sterilized package. All components of the tubing set are summarized in Figure 7.1.

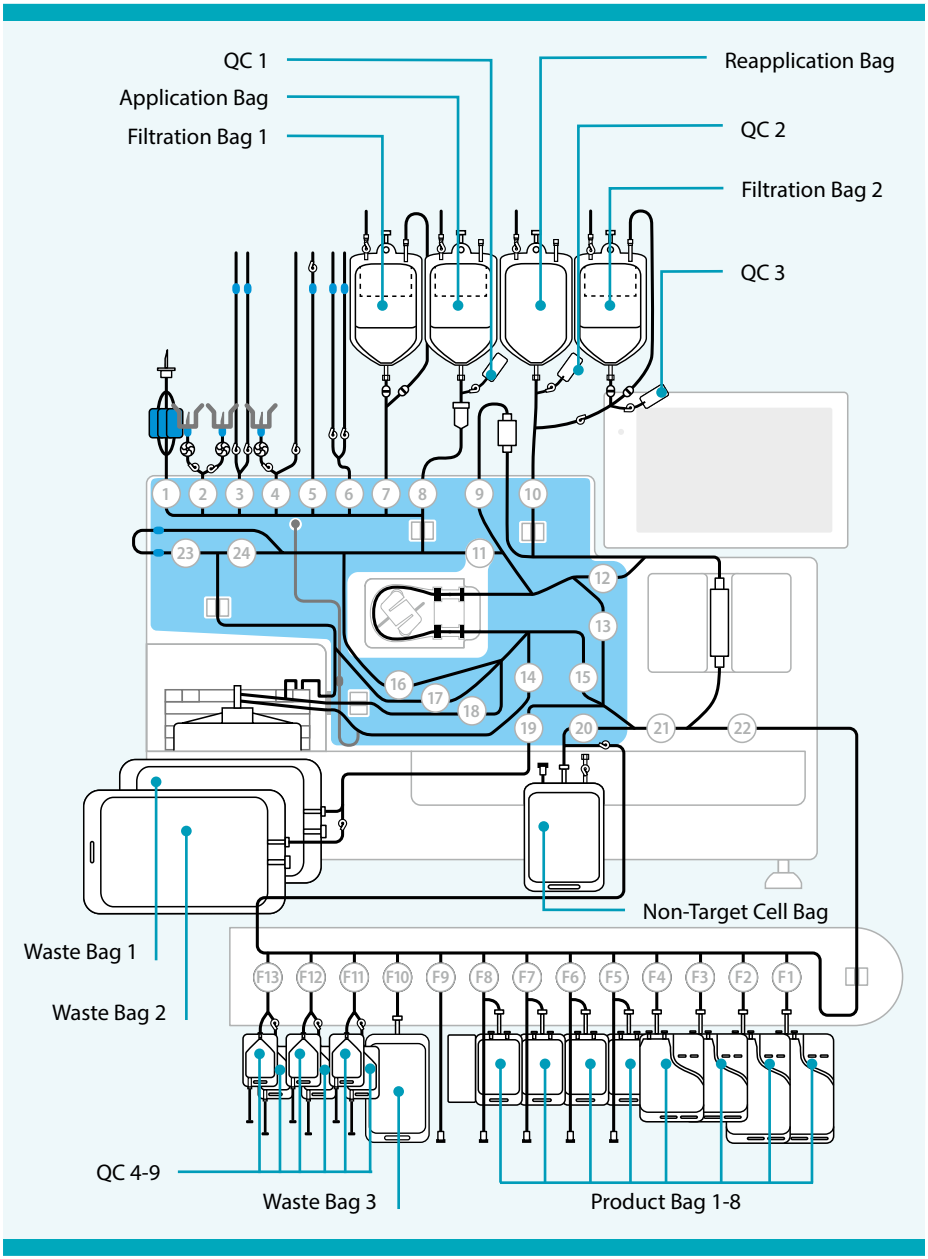


Figure 7.1: Components of the CliniMACS Prodigy TS 521

7.3.2 Installation steps

This section guides step by step through the installation of all tubing set components (see Screen 7.7 to Screen 7.34).

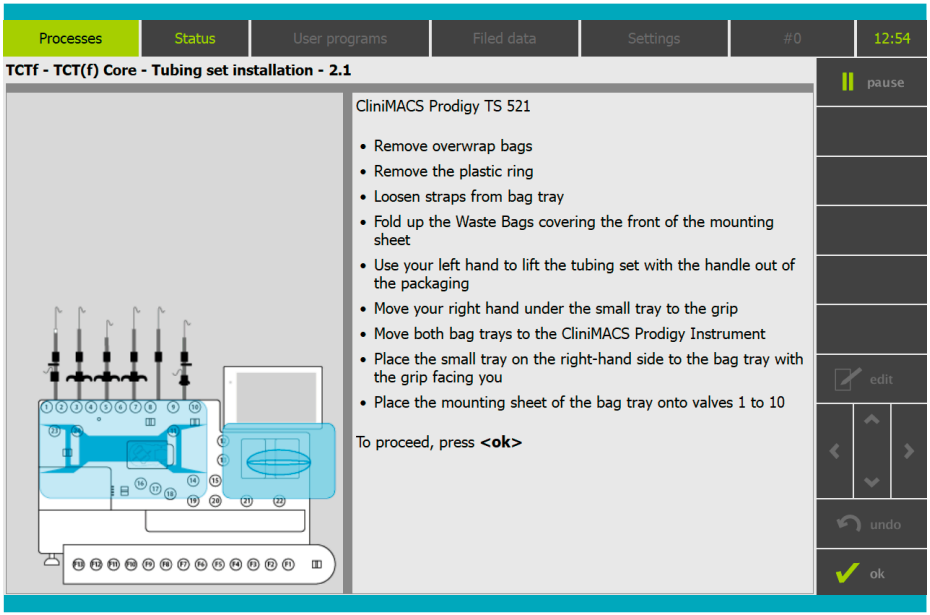
Each screen shows the written instructions supported by an informative image. Blinking and orange features in an image indicate areas of attention.

To return to a previous step at any step during the installation, tap <undo>.

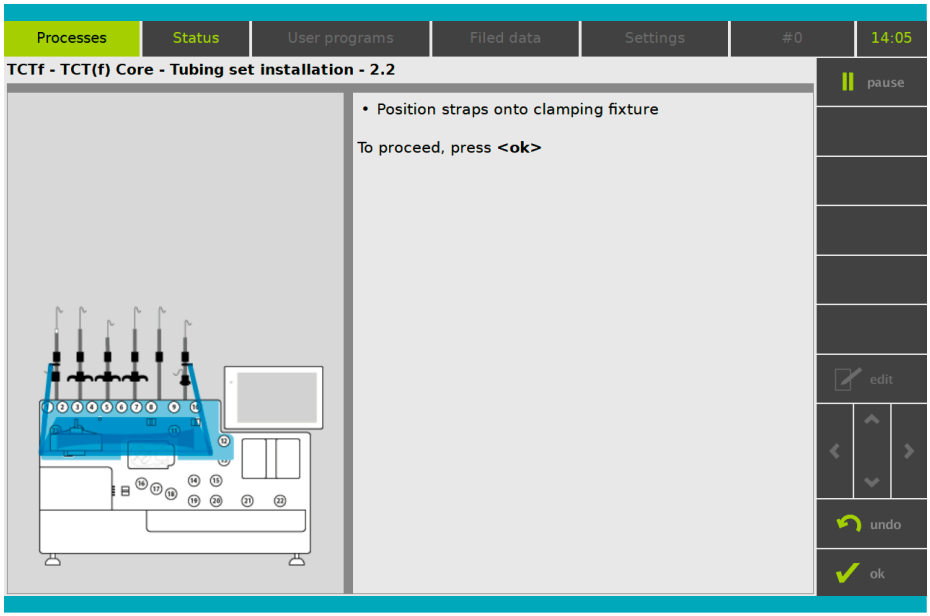
⚠ WARNING

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.

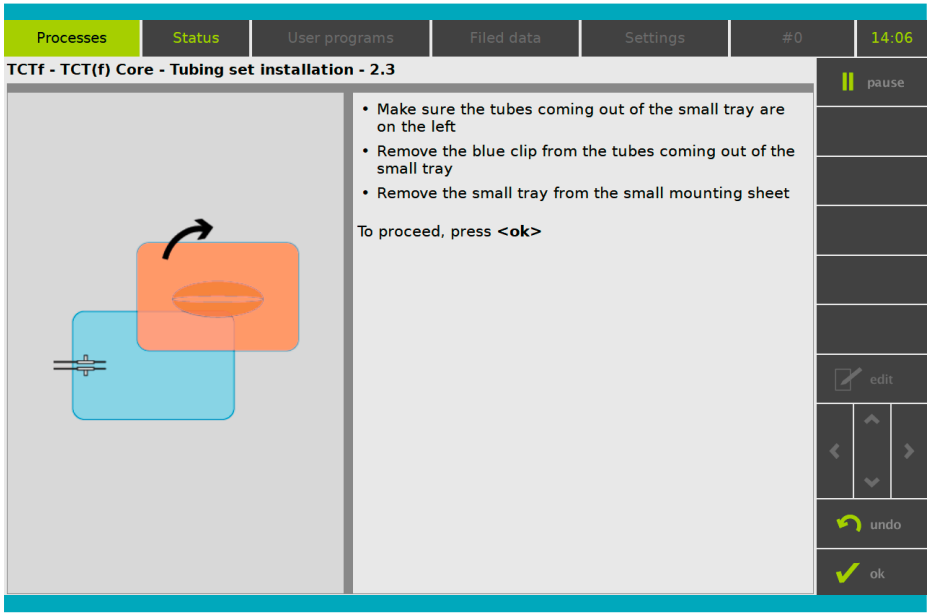
- Use the tubing set only if package is undamaged and sealed.



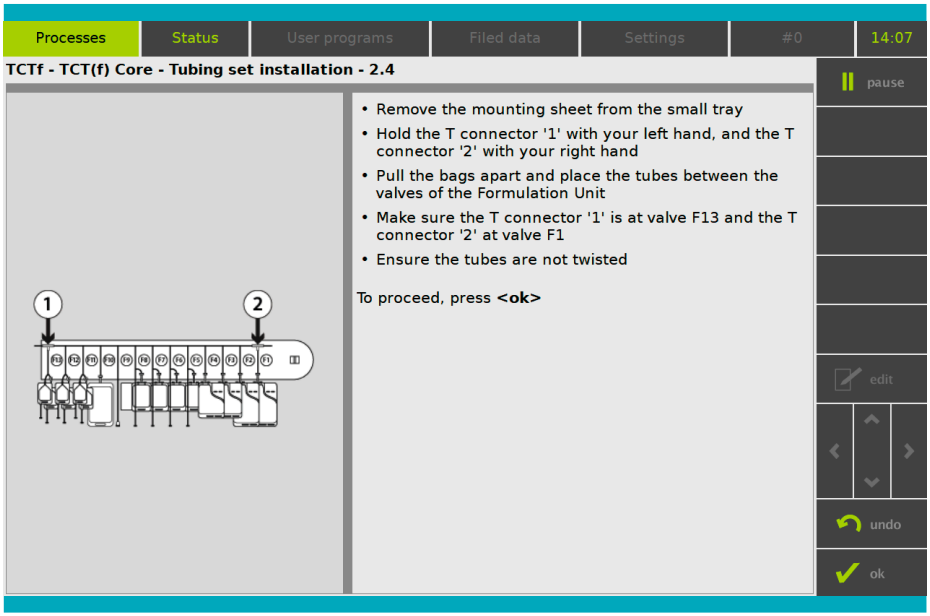
Screen 7.7: Installation of bag tray and mounting sheet



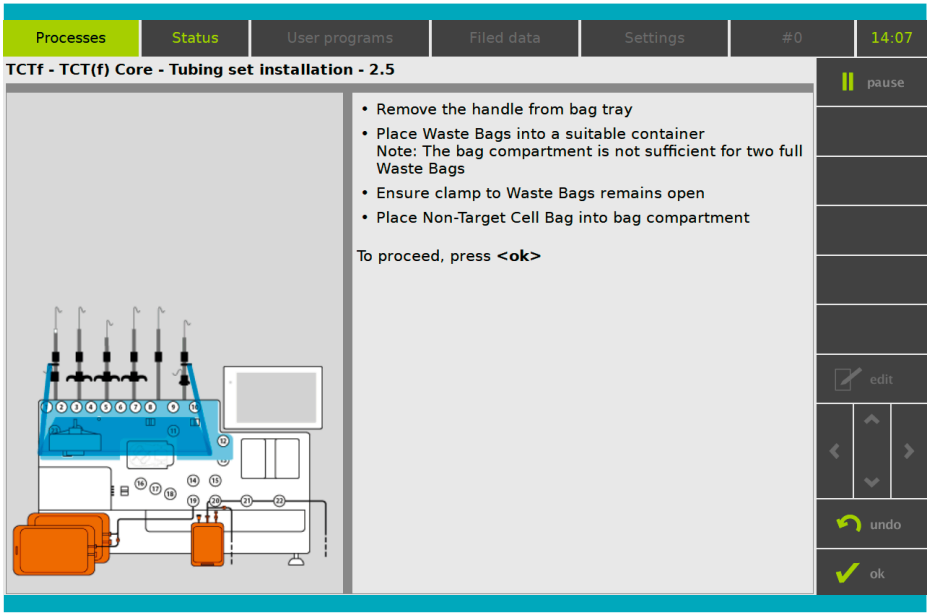
Screen 7.8: Installation of the position straps



Screen 7.9: Guidance for installation of the small tray



Screen 7.10: Placement of the Formulation part onto the Formulation Unit



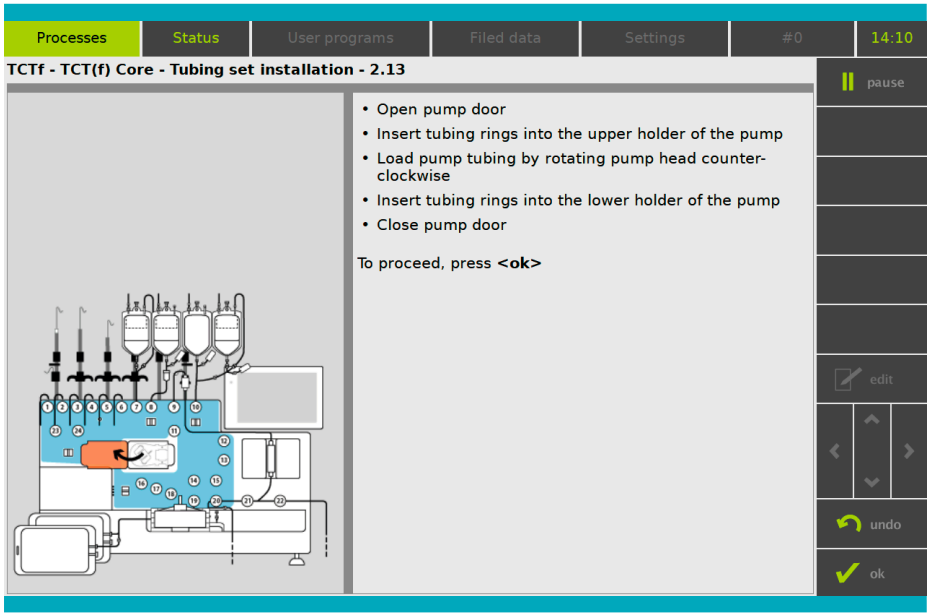
Screen 7.11: Placement of bags into bag compartment, closure of clamps and removal of the handle

IMPORTANT

The Waste Bags must be safely placed outside of the bag compartment in a suitable container next to or below the CliniMACS Prodigy.

The CliniMACS Prodigy TS 521 contains two Waste Bags, which do not fit both into the bag compartment when completely filled. Therefore, use one of the following options:

- Store one bag in the bag compartment and keep the clamp on the other bag closed until replacement is required.
- Put both bags in a separate fitting bag compartment on the left-hand side of the CliniMACS Prodigy to be filled simultaneously.



Screen 7.12: Insertion of separation column into magnet unit

Figure 7.2 shows how to insert the separation column into the column holder of the magnet unit.

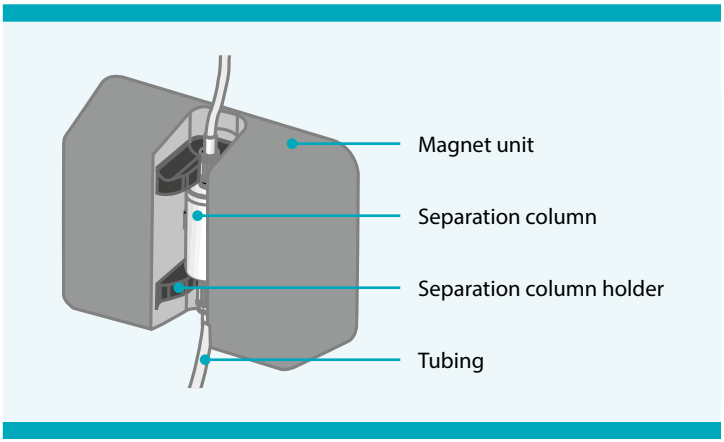
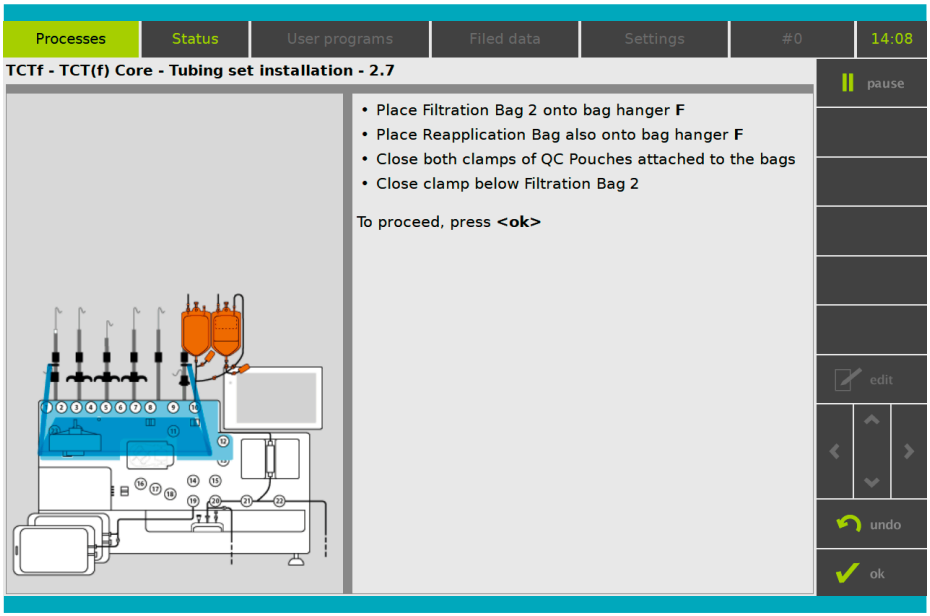


Figure 7.2: Separation column inserted into magnet unit

⚠ WARNING

Risk of injury. If the separation column is inserted or removed while the magnet unit is switched on, then there is the risk of personal injury.

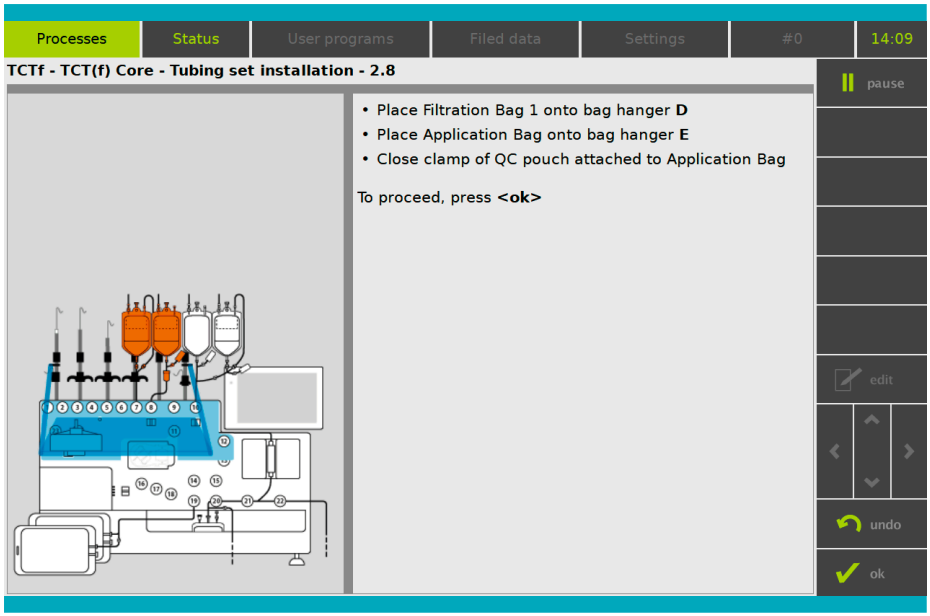
- Only insert or remove the separation column when the magnet unit is switched off.



Screen 7.13: Installation of Reapplication Bag and Filtration Bag 2

IMPORTANT

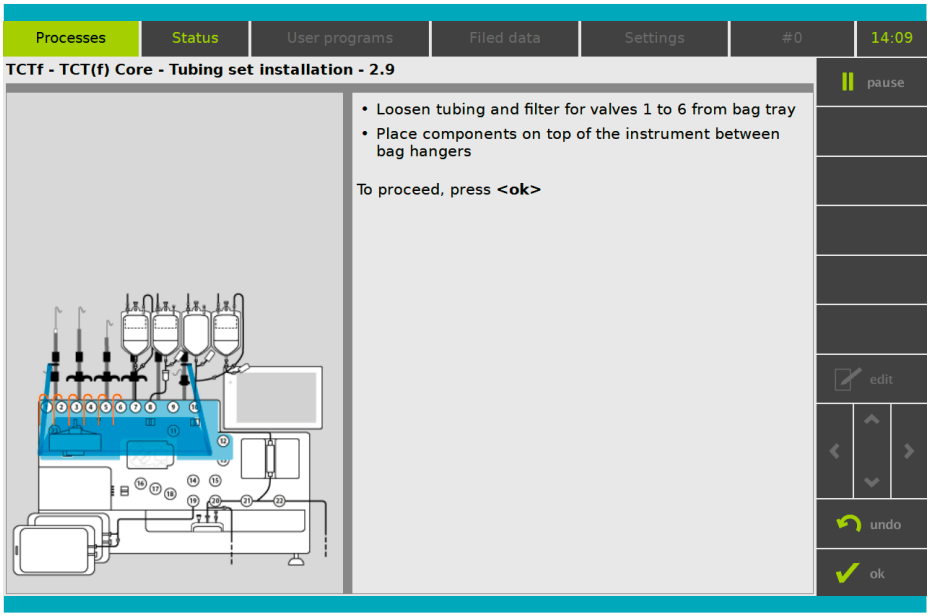
Ensure that both clamps of the QC Pouches on the bags are closed. Also ensure that the clamp below Filtration Bag 2 is closed.



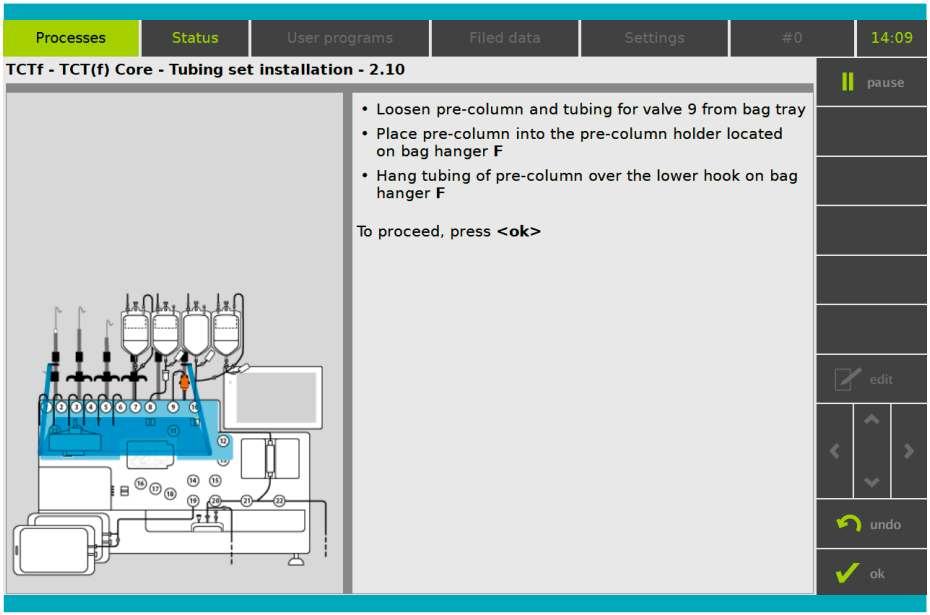
Screen 7.14: Installation of Filtration Bag 1 and Application Bag

IMPORTANT

Ensure that the clamp on the QC Pouch attached to the Application Bag is closed.



Screen 7.15: Placement of tubing set components between bag hangers



Screen 7.16: Installation of pre-column into pre-column holder on bag hanger (F)

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

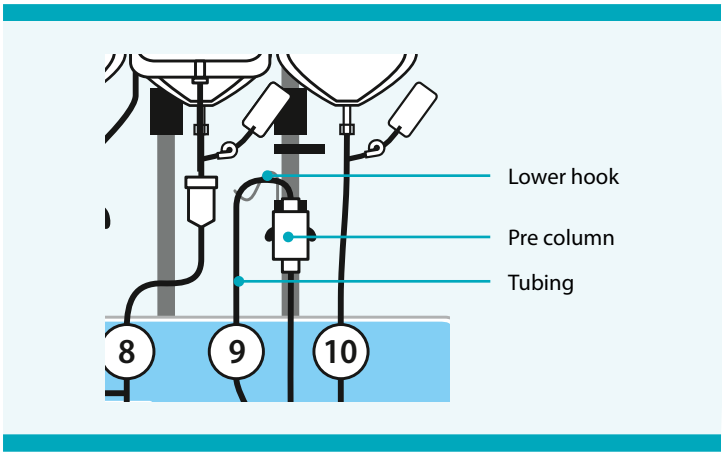
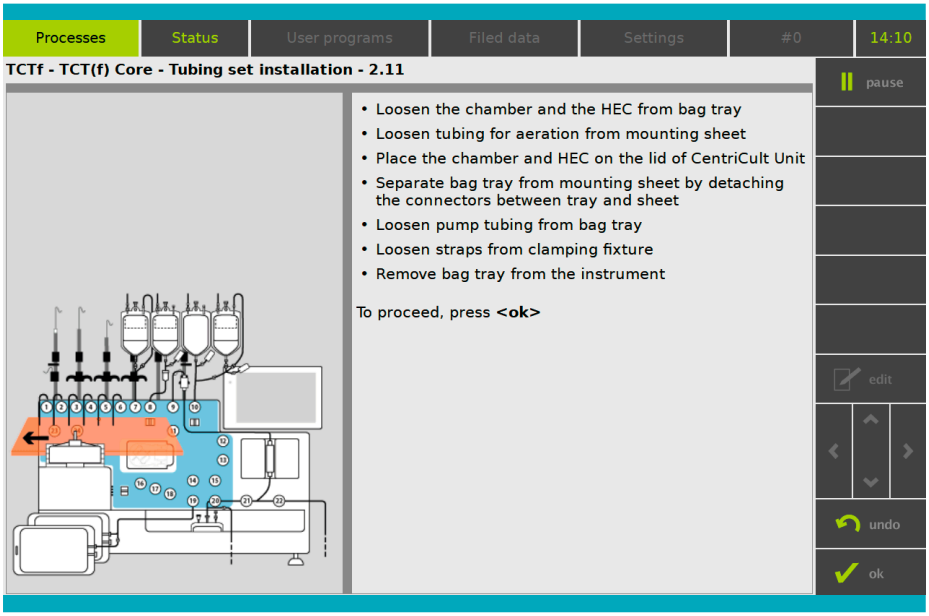
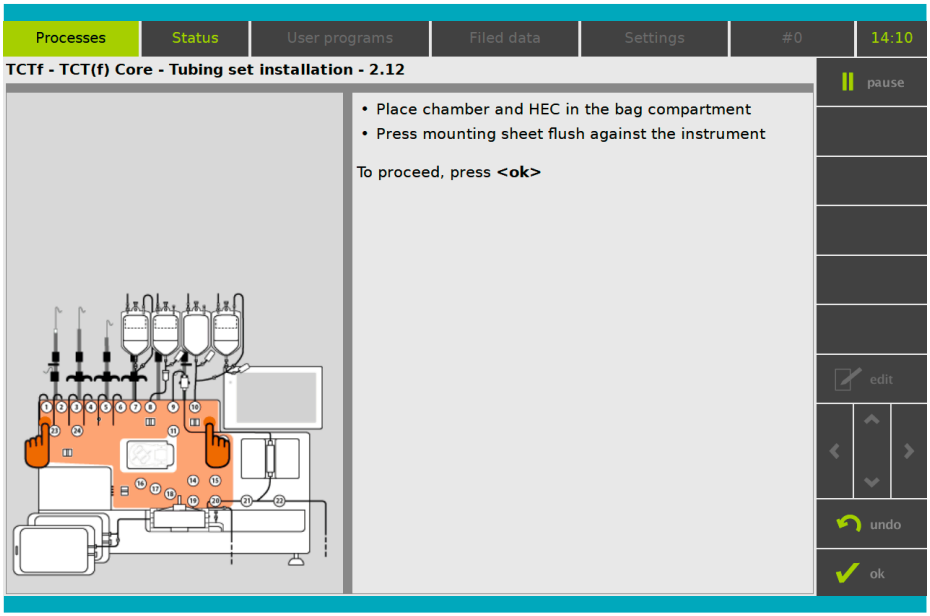


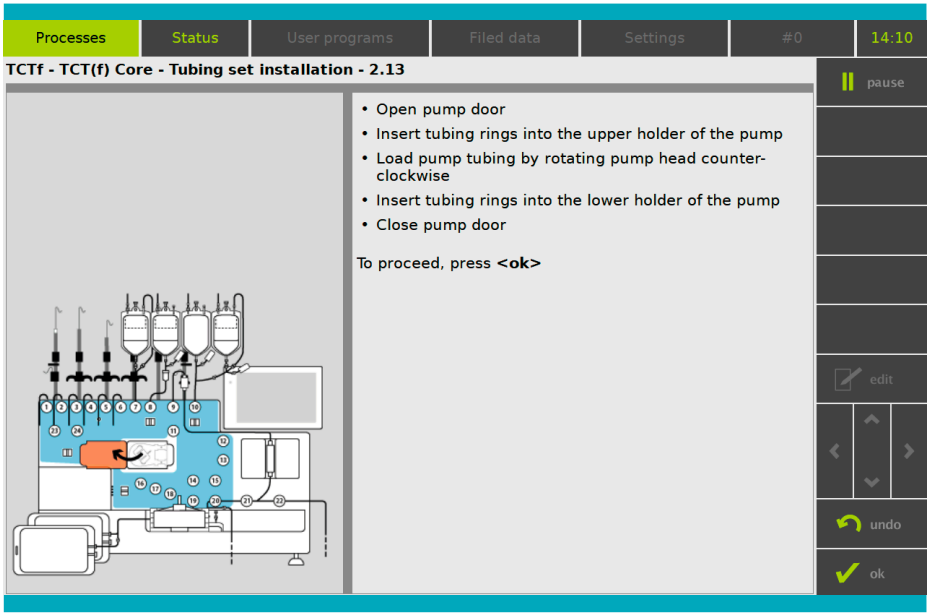
Figure 7.3: Guidance of pre-column-associated tubing



Screen 7.17: Removal of bag tray from instrument



Screen 7.18: Placement of chamber and HEC



Screen 7.19: 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 of the pump.
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 clockwise and counterclockwise to ensure the pump head moves freely.

If necessary, the tubing can be unloaded by lifting the lower end of the tubing and turning the pump head clockwise until the tubing is released.

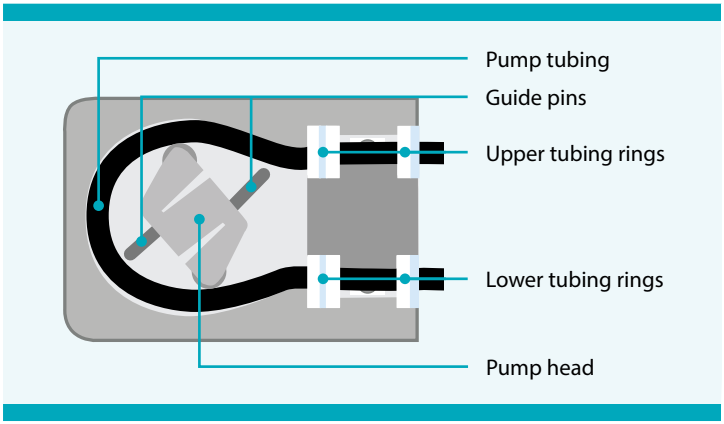
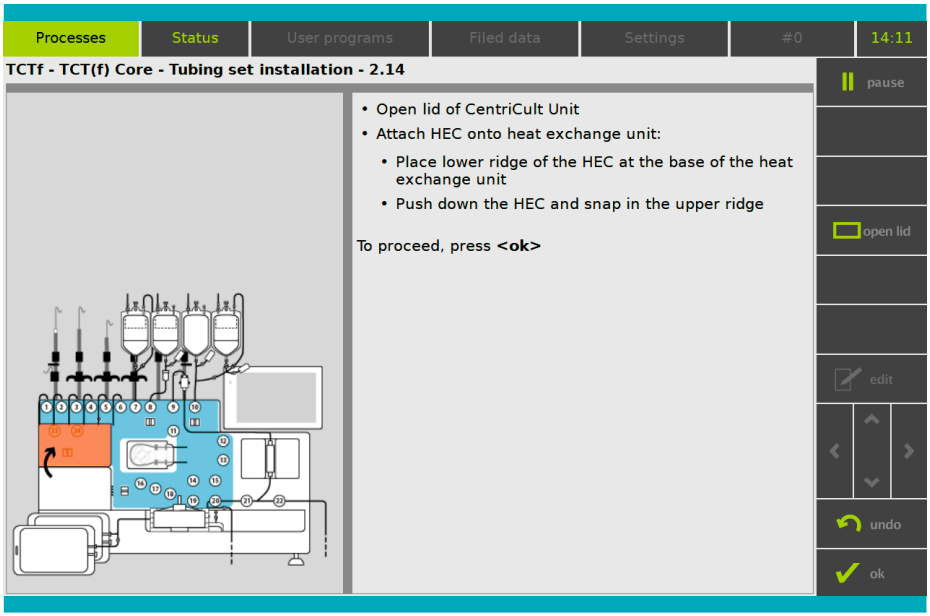


Figure 7.4: Pump tubing inserted into pump

The CentriCult Unit lid will unlock automatically for the installation of the Heat Exchange Cartridge (HEC) and chamber (see Figure 7.5 to Figure 7.7). If the lid does not unlock automatically, tap **<open lid>** on the menu bar.



Screen 7.20: Installation of HEC onto heat exchange unit

Step-by-step installation of HEC onto heat exchange unit

Figure 7.5 to Figure 7.7 illustrates the installation of the HEC onto the heat exchange unit. Confirm the HEC attaches tightly to the heat exchange unit to allow heating and cooling of liquid inside the HEC.

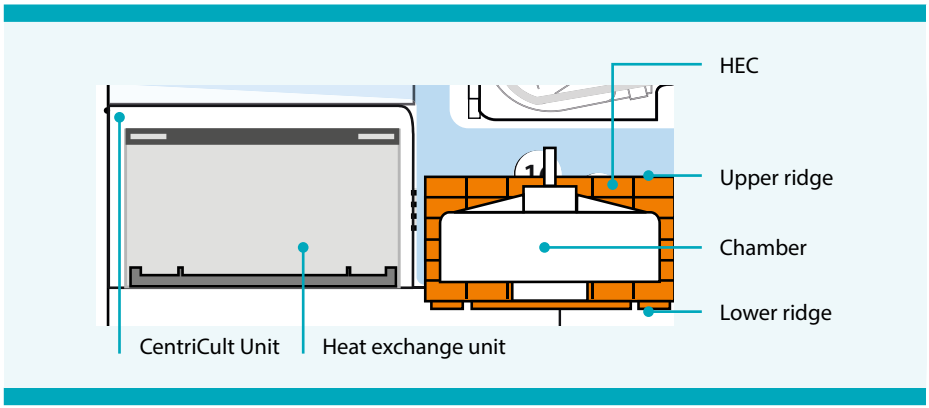


Figure 7.5: Step 1 – Loosen the HEC from chamber

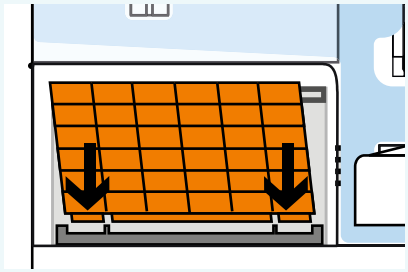


Figure 7.6: Step 2 – Place lower ridge of the HEC at the base of heat exchange unit.

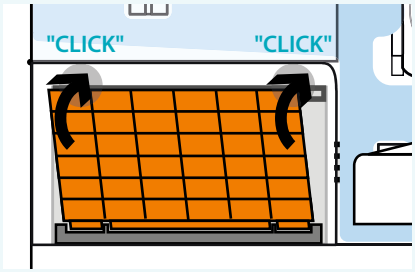
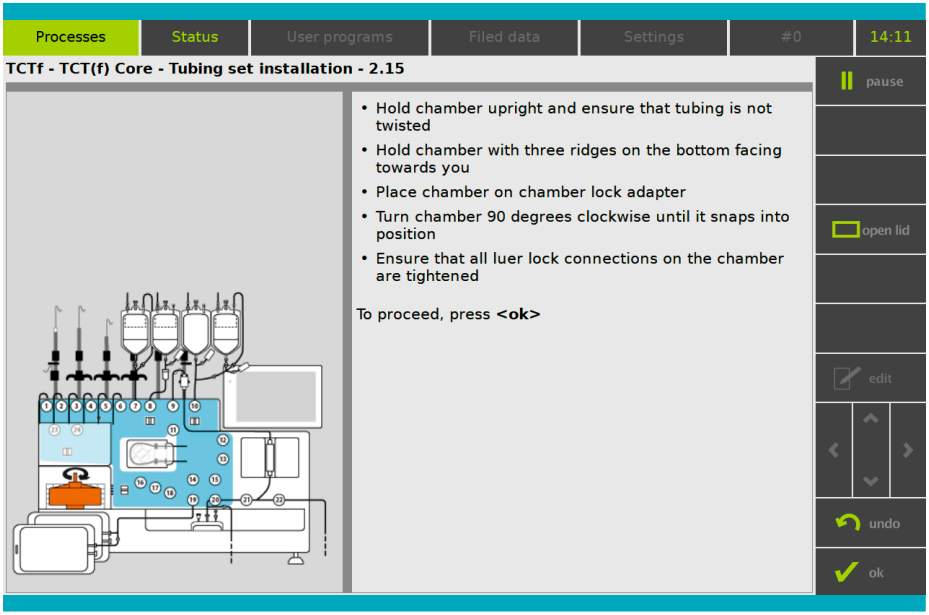


Figure 7.7: Step 3 – Push down the HEC and snap in upper ridge.



Screen 7.21: Installation of chamber into CentriCult Unit

After inserting the HEC, install the chamber according to instructions on the screen (see Screen 7.21).

Figure 7.8 shows the components of the CentriCult Unit.

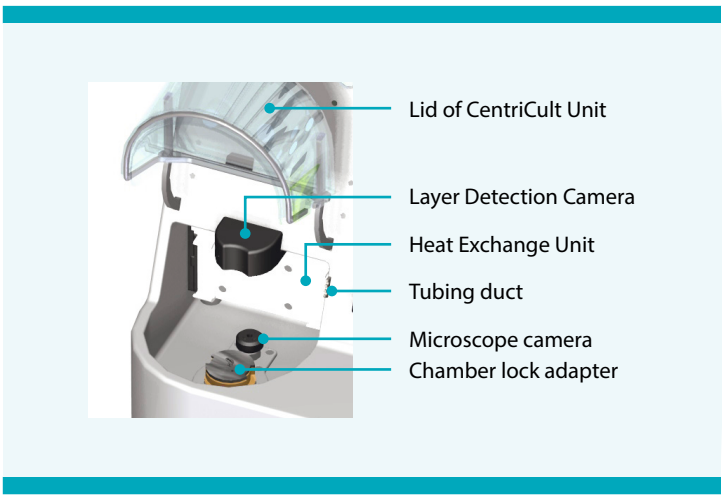


Figure 7.8: Components of the CentriCult Unit

IMPORTANT
The chamber has a scale bar on its lid. This scale bar has to point towards the user when placed on the chamber lock adapter.

IMPORTANT
Before positioning the chamber onto the chamber lock adapter, confirm 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 correctly into position.

⚠ CAUTION

Risk of process failure. An incorrectly installed chamber can cause a process failure. Ensure that the chamber is tightly locked in position.

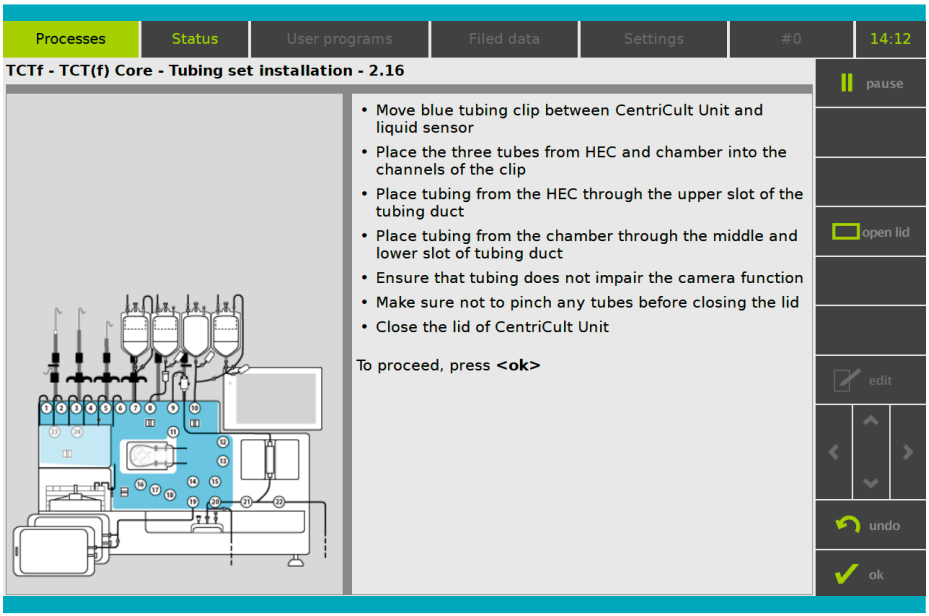
- Do not use the tubing set if the chamber cannot be installed properly.

⚠ CAUTION

Risk of process failure. Contact between the chamber and the tubes leading to HEC can cause tube destruction during chamber rotation.

- Ensure that chamber does not touch tubes leading to HEC.

If a twist or bending of the chamber tubing is recognized after the chamber is already locked, follow the instructions in the Important section connected to Screen 7.30 and correct the tubing position during that step.



Screen 7.22: Guidance of tubings from HEC and chamber through slots of tubing ducts

IMPORTANT
Before closing the lid, ensure that no tubing is pinched by the lid.

Figure 7.9 illustrates how to insert the two chamber tubing lines through the tubing duct.

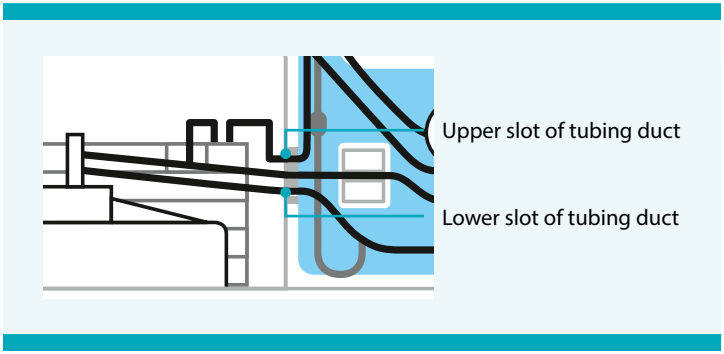
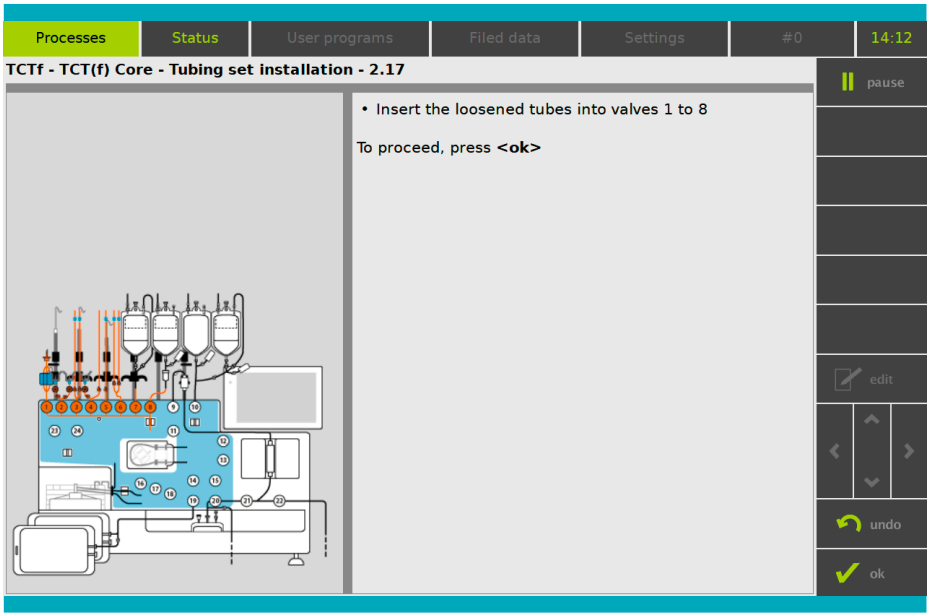


Figure 7.9: Guidance of tubing through tubing duct



Screen 7.23: Insertion of tubing into valves 1 to 8

Figure 7.10 shows how the tubing should be inserted correctly into the respective valve.

Insert the tubing only into open valves (when the valve button is pressed down). Otherwise, the tubing will not fit correctly.

If a tubing has to be adjusted, press the valve button to open the valve before adjustment.

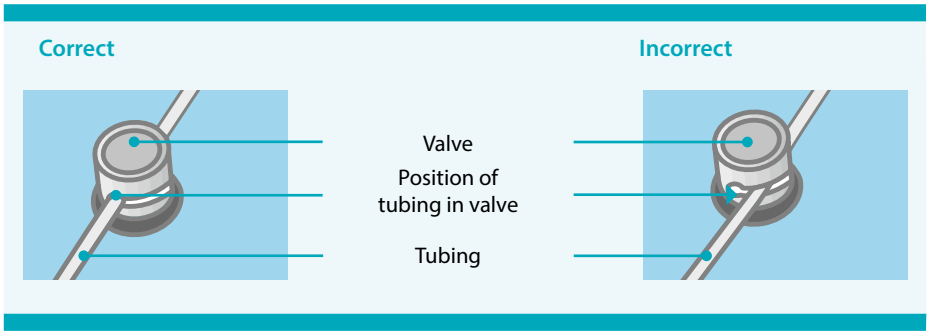
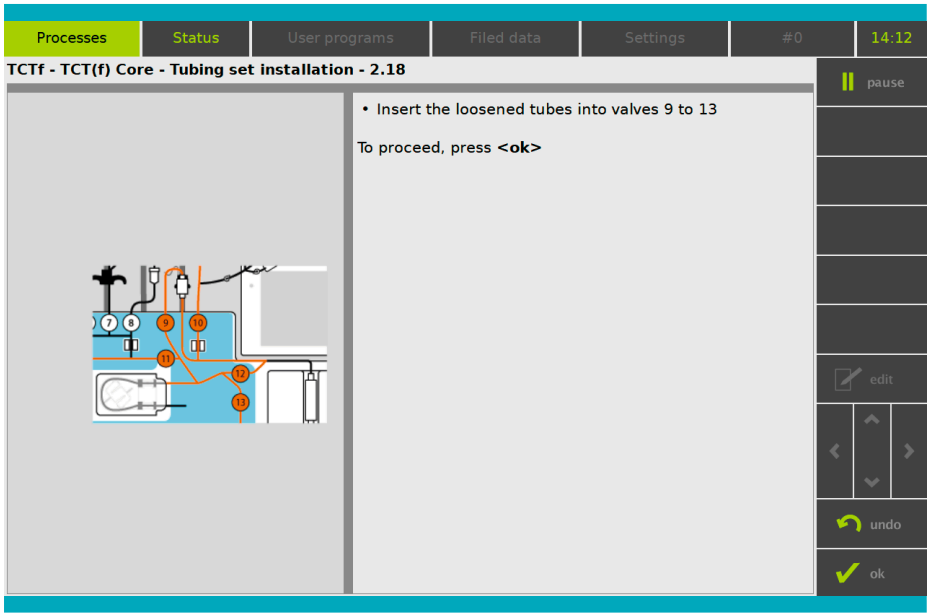


Figure 7.10: Insertion of tubing into valves



Screen 7.24: Insertion of tubing into valves 9 to 13

Figure 7.11 shows how to insert the tubing correctly into valve 12.

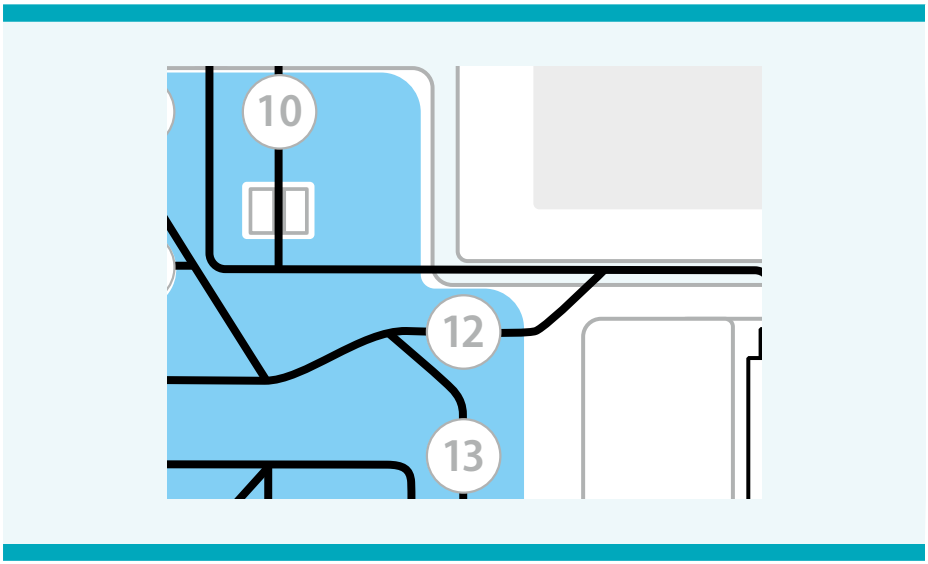
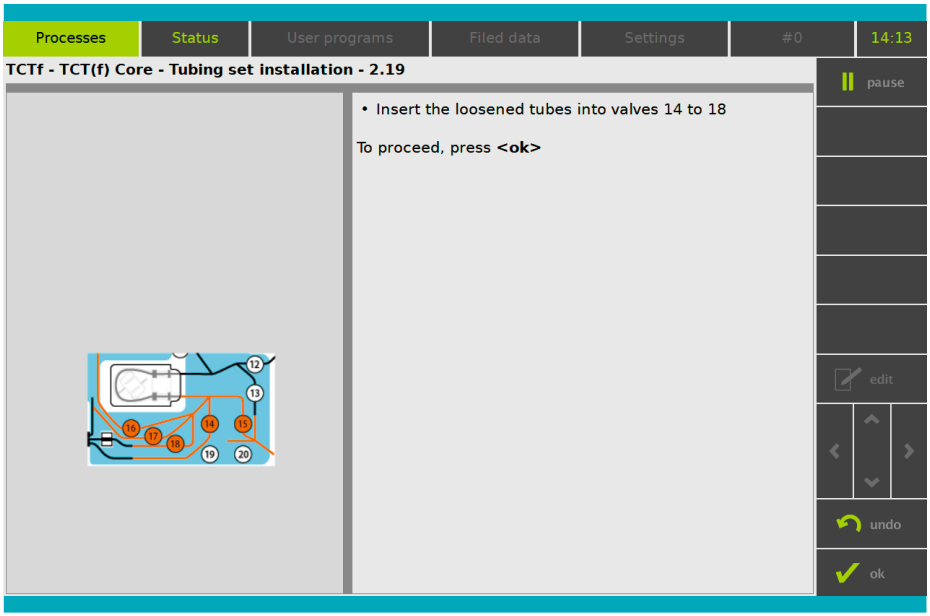
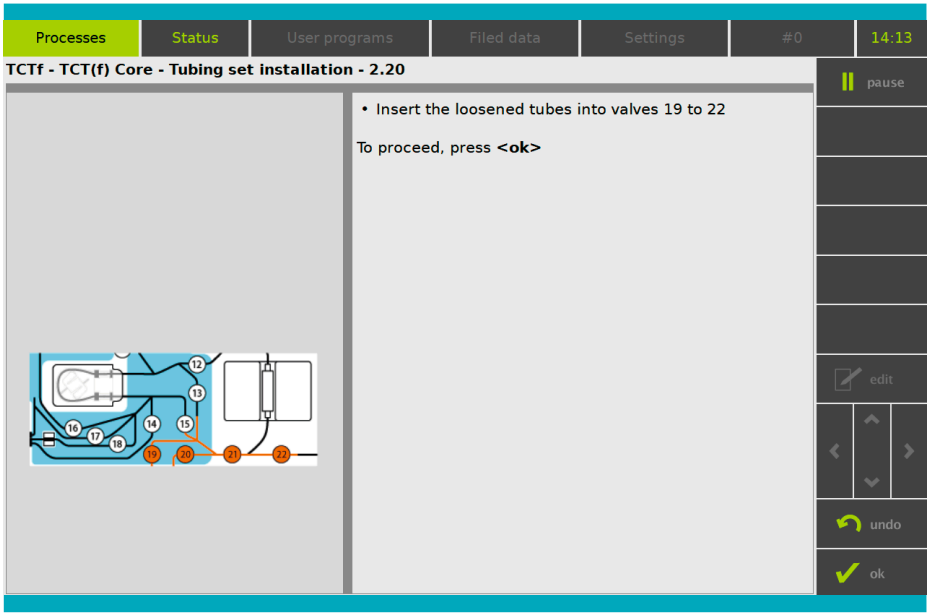


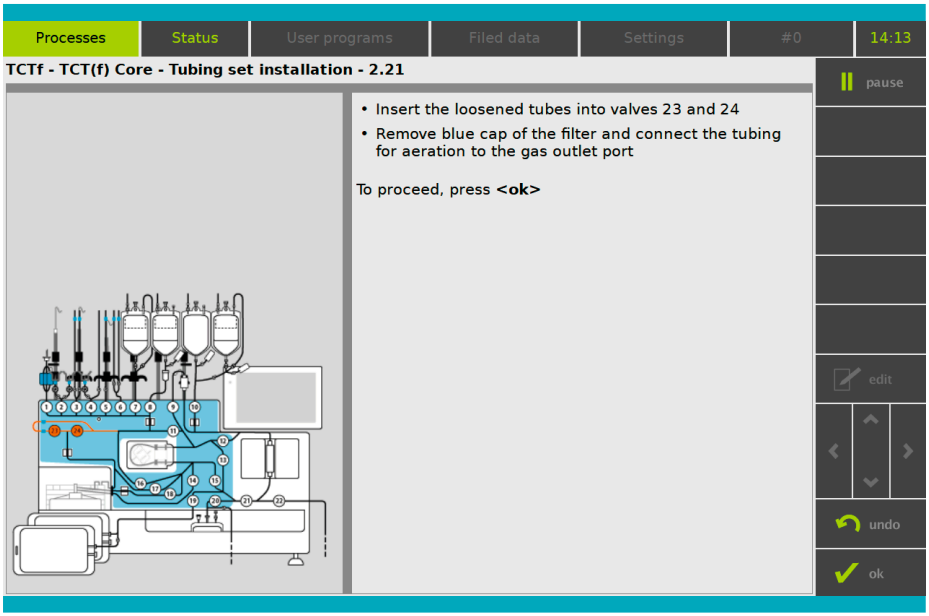
Figure 7.11: Guidance of tubing for separation column and valves 12



Screen 7.25: Insertion of tubing into valves 14 to 18



Screen 7.26: Insertion of tubing into valves 19 to 22

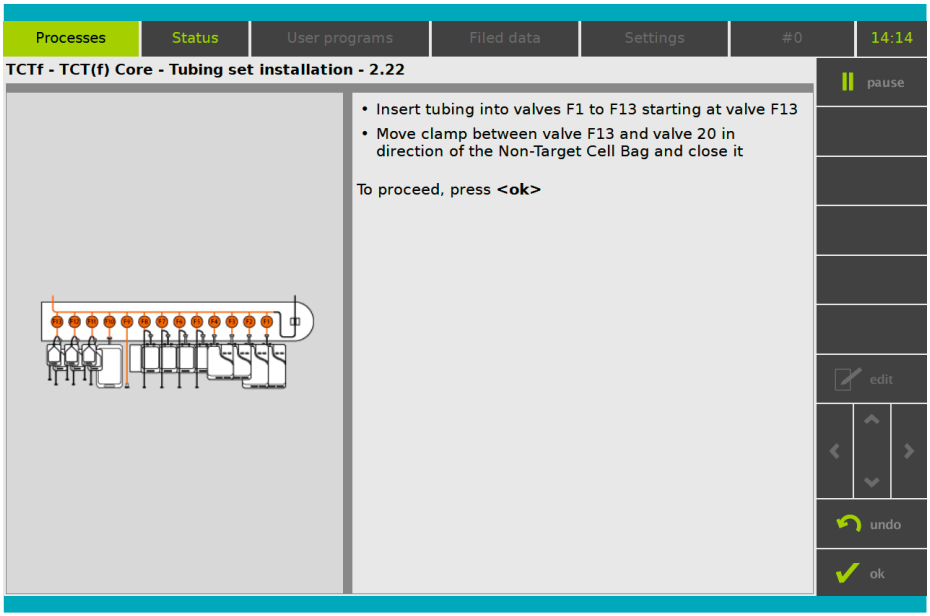


Screen 7.27: Insertion of tubing into valves 23 and 24 and connection of tubing for aeration to the gas outlet port

⚠ CAUTION

Risk of process failure. Improper gas flow can cause process failure.

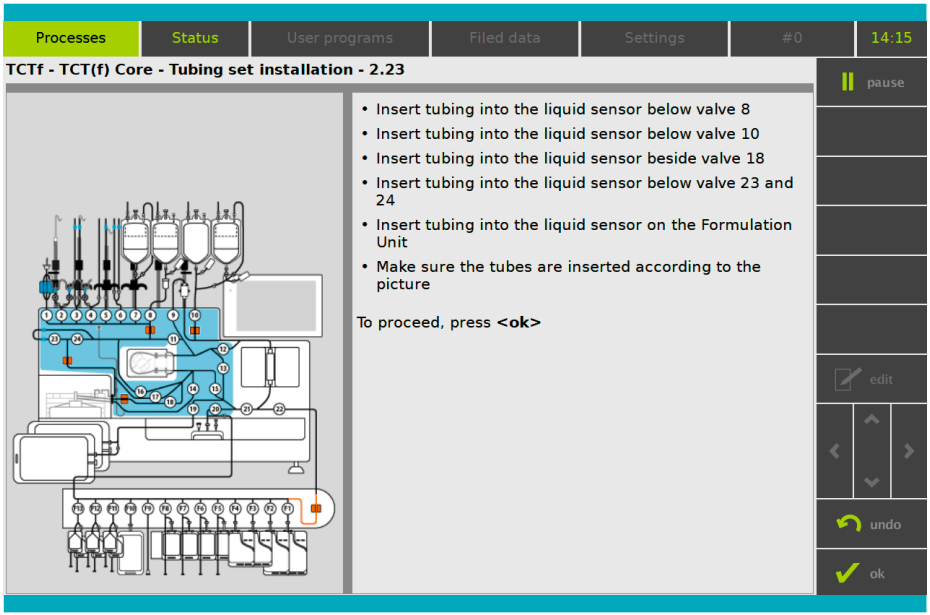
- The tubing for aeration should be tightly connected to the gas outlet port to ensure a proper gas flow into the cultivation chamber.



Screen 7.28: Insertion of tubing into valves F1 to F13

IMPORTANT

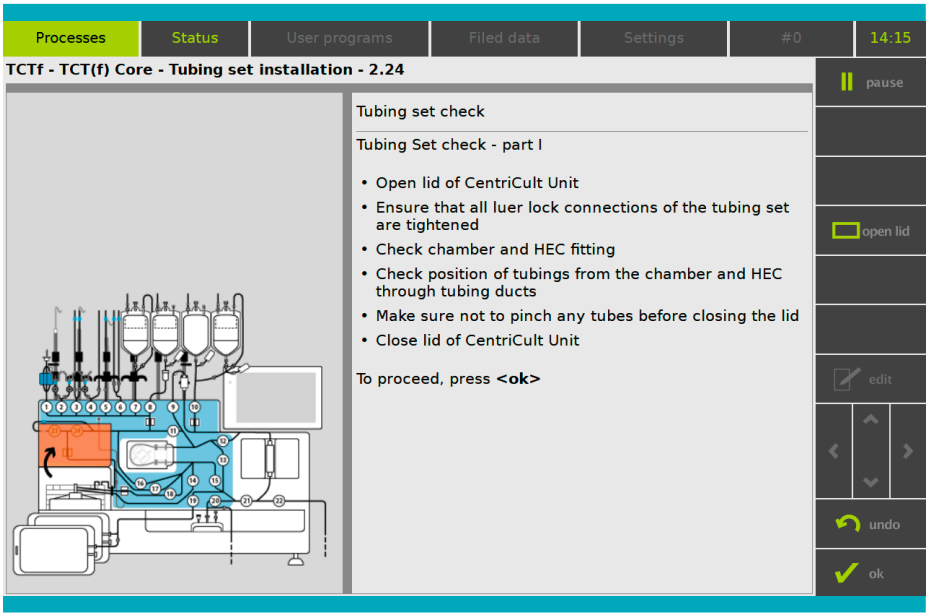
Ensure that the clamp between valve F13 and valve 20 in the direction of the Non-Target Cell Bag is closed.



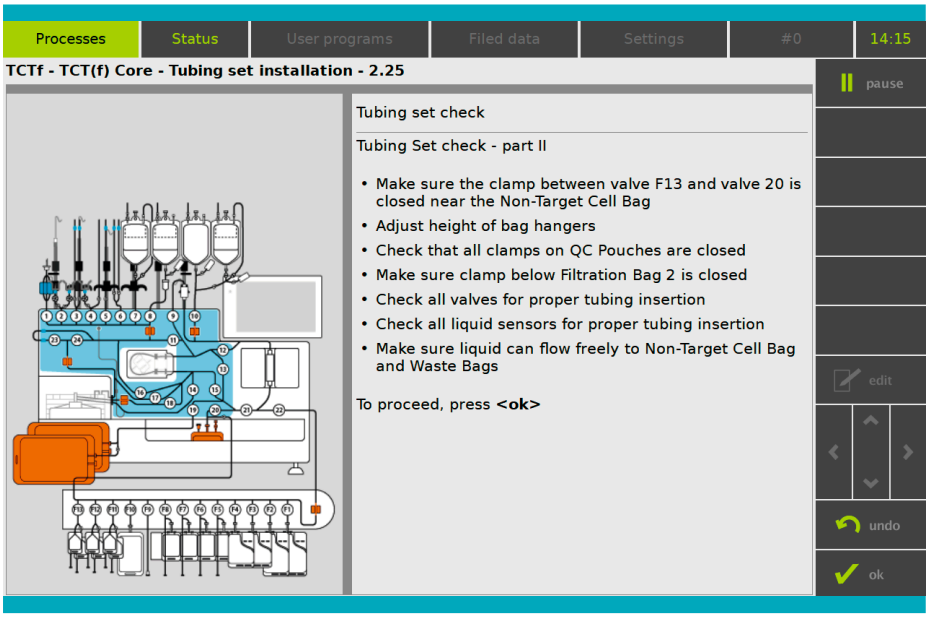
Screen 7.29: Insertion of tubing into liquid sensors

IMPORTANT

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



Screen 7.30: Tubing set check – part I



Screen 7.31: Tubing set check – part II

IMPORTANT

Review all tubing for kinks or severe bending that could restrict the flow of liquid through the tubing set. If a tubing position has to be adjusted, press the valve button to open the respective valve beforehand (see Figure 7.10).

If necessary, raise or lower the bag hanger to adjust the height of the bag. Ensure that the bags are positioned high enough to prevent severe bending of the tubing and low enough to avoid the tubing or connections being stretched.

In addition, verify the tightness of all Luer Lock connections at the tubing set including both Luer locks of the chamber.

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

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 chamber needs to be removed, tap **<open lid>** on the toolbar. Wait until the lid opens. Turn the chamber 90 degrees counterclockwise to remove it from the drive shaft.

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

When the tubing set installation is complete, all valves will open and close twice to verify proper functionality. In addition, the forward and backward movement of the magnet inside the magnet unit is tested. If a valve or the magnet does not operate correctly, contact Miltenyi Biotec Technical Support.

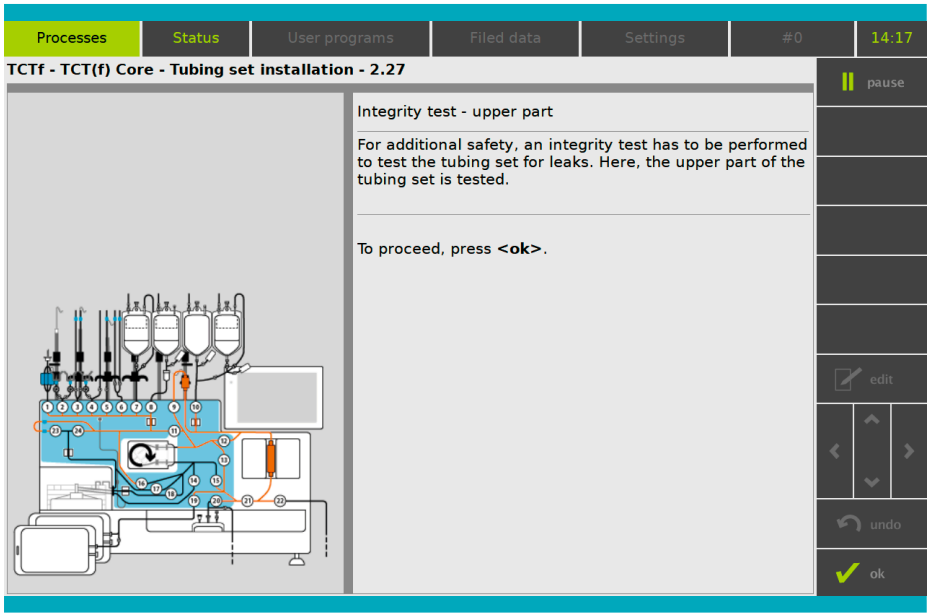
IMPORTANT

For additional safety, an integrity test is strongly recommended to test the tubing set for leaks. The test consists of three automated sequences that apply controlled overpressure separately to the upper, lower and Formulation Unit part of the tubing set.

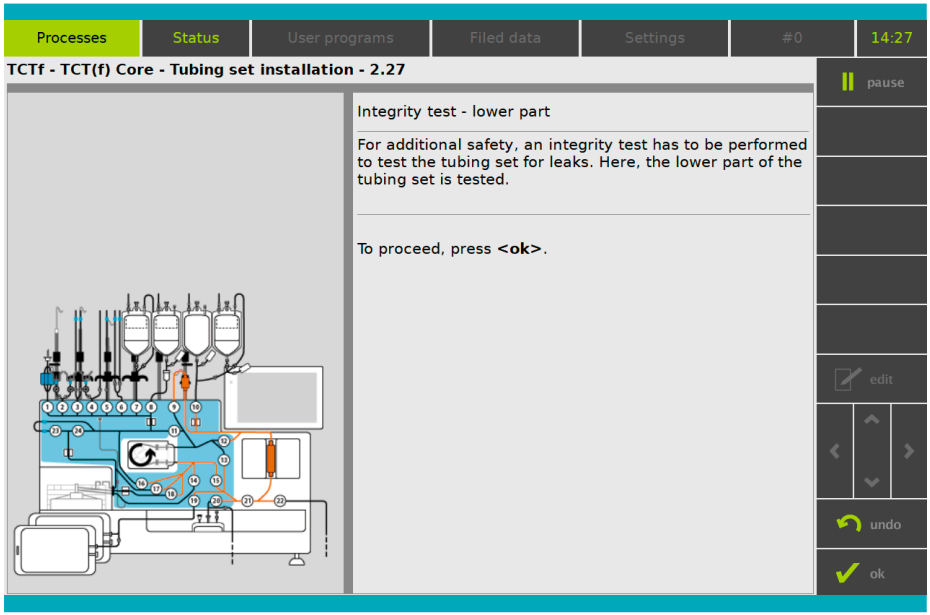
Follow the instructions on the screen to start the integrity test for the tubing set.

It is not recommended to tap **<no>** and skip the integrity test in the following pop-up.

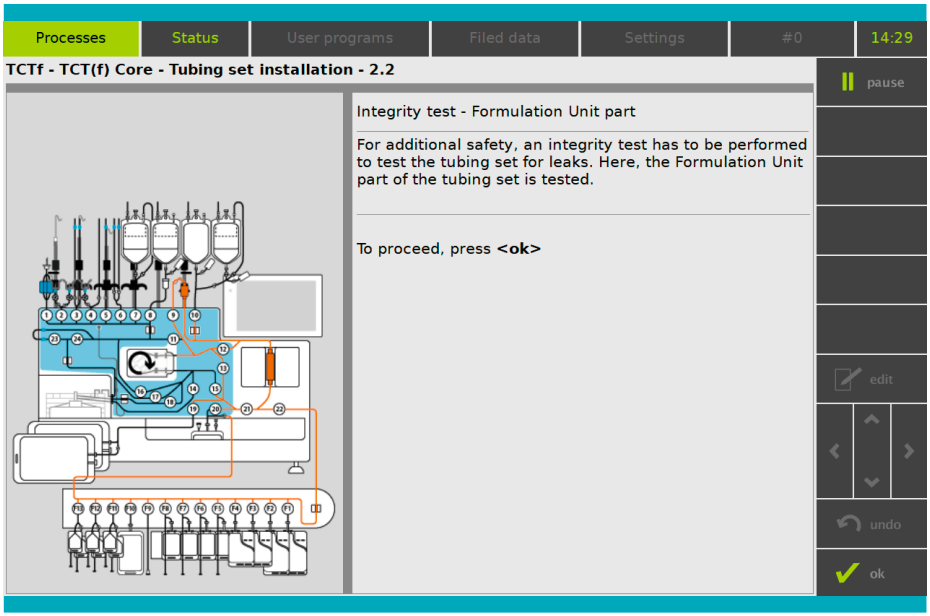
Perform separate integrity tests for the upper, lower and Formulation Unit part of the tubing set.



Screen 7.32: Integrity test for upper part



Screen 7.33: Integrity test for lower part



Screen 7.34: Integrity test for the Formulation Unit part

⚠ WARNING

Risk of contamination. A failed integrity test can indicate a potential leakage in the tubing set which carries the risk of contamination. If a tubing set fails the integrity test, carefully verify that all tubing is correctly inserted into the appropriate valves. Repeat the integrity test after verification of proper tubing set installation.

- Do not use the tubing set, if it is not possible to pass upper, lower and Formulation Unit integrity test.

Contact Miltenyi Biotec Technical Support for assistance, if required.

7.4 Tubing set priming

7.4.1 Connection of medium and buffer

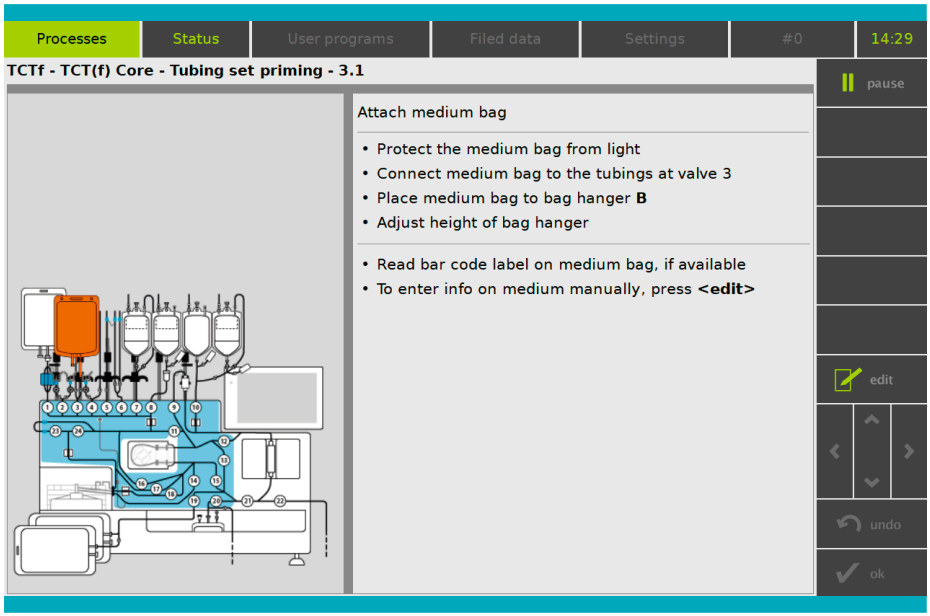
Refer to chapter 6 ´Preparative steps´ of this user manual for the preparation medium and process buffer.

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.
- If several bags weighing more than 5 kg in total are to be connected, they must be divided among several bag hangers.

Screen 7.35 to Screen 7.43 will guide through the priming phase.



Screen 7.35: Connection of medium bag

IMPORTANT

UV light could lead to adverse effects on the TexMACS GMP Medium. Protect the TexMACS GMP Medium from UV light using the provided protection bag (yellow) before connection to the tubing set.

To connect the medium bag to the tubing set on valve 3 by sterile welding, use a sterile tubing welder placed next to the instrument.

Place the medium bag on bag hanger B.

Read the barcode label on the medium bag with the barcode reader. To enter part number (P/N) and batch code (LOT) manually with the keyboard, tap <edit>.

IMPORTANT

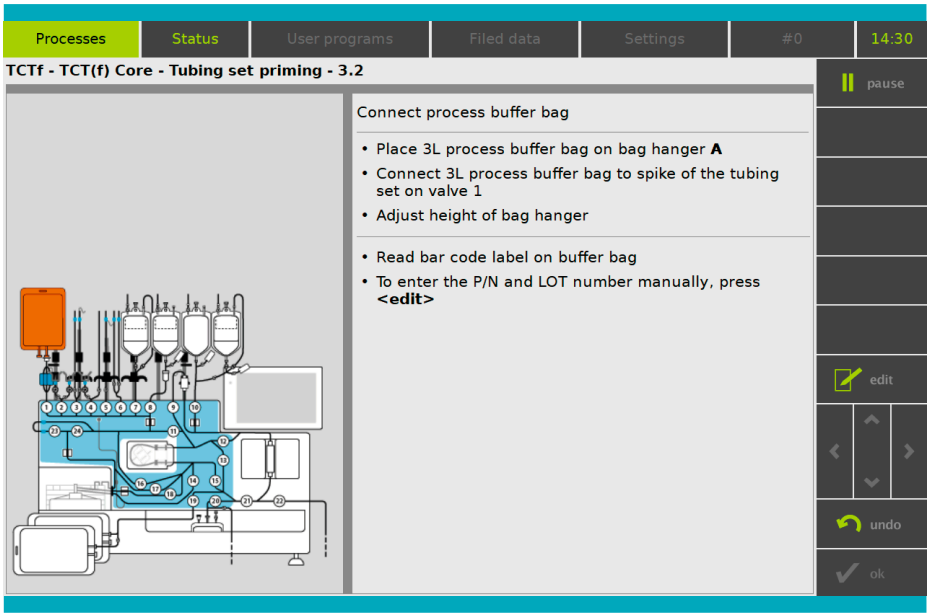
Confirm that the clamp and welding seam of the medium bag is open at this point.

To enter information on supplements, tap <edit> .

If necessary, raise or lower the hanger to adjust the height of the bag hanger. Ensure that the bag is positioned at a suitable height to prevent severe bending or overstretching of the tubing.

IMPORTANT

It is recommended to use TexMACS GMP Medium for the T Cell Transduction and Automated Formulation. Using other medium could result in a lower performance.



Screen 7.36: Connection of process buffer bag

To connect the process buffer bag to the tubing set on valve 1:

- Place the process buffer bag on bag hanger A.
- Uncap the spike of the tube connected to valve 1.
- Spike it into the process buffer bag.
- Ensure that the filter is positioned in an upright position.

Alternatively, the process buffer bag can be connected to the tubing set by sterile welding. Ensure that the welding seam is opened.

Read the barcode label on the process buffer bag. To enter the part number (P/N) and lot number (LOT) manually, tap <edit>.

To enter information on the HSA, tap <edit>.

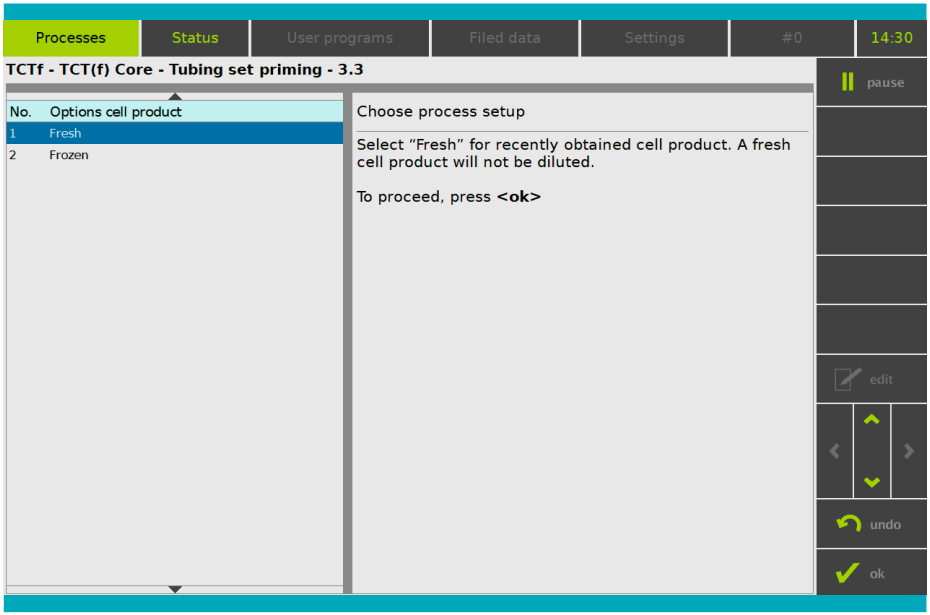
If necessary, raise or lower the bag hanger to adjust the height of the hanger. Ensure that the bag is positioned at a suitable height to prevent severe bending or overstretching of the tubing.

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

Bag hanger ID	Bag
A	3 000 mL process buffer bag
B	2 000 mL medium bag
C	–
D	Filtration Bag 1
E	Application Bag
F	Reapplication Bag and Filtration Bag 2

Table 7.1: Positions of bags on bag hangers during priming and enrichment

7.4.2 Selection of fresh or frozen cell product

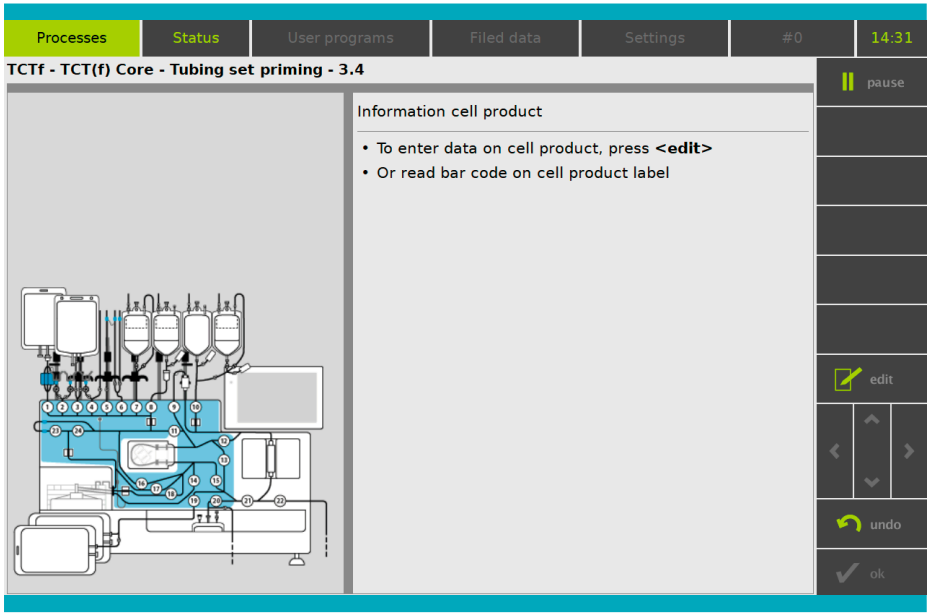


Screen 7.37: Selection of fresh or frozen starting cell product

Select "Fresh" for fresh leukapheresis, whole blood, or peripheral blood mononuclear cells (PBMCs) or select "Frozen" for a frozen leukapheresis product, as starting cell product. Confirm with <ok>.

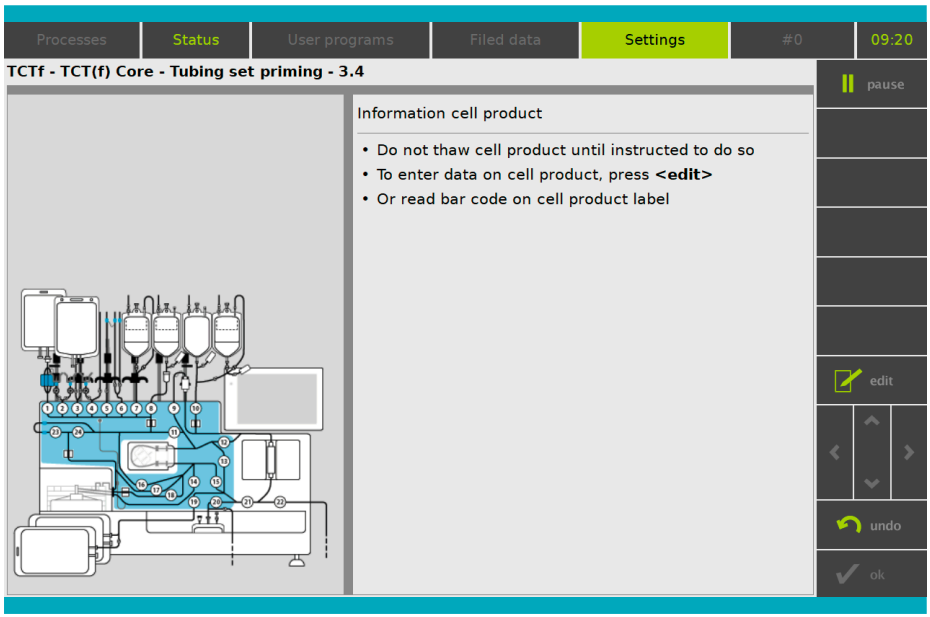
Please note that the use of a fresh or frozen leukapheresis product as starting material is recommended as the default protocol has been verified with fresh or frozen leukapheresis material.

Selection of fresh cell product



Screen 7.38: Information of fresh cell product

To enter the information of the cell product or read the barcode label, tap <edit> (see Screen 7.38). The transfer of the cell product will happen later during the process (see section 7.5.3 ´Prepare cell separation´).



Screen 7.39: Information of frozen cell product

Dilution of frozen cell product

⚠ CAUTION

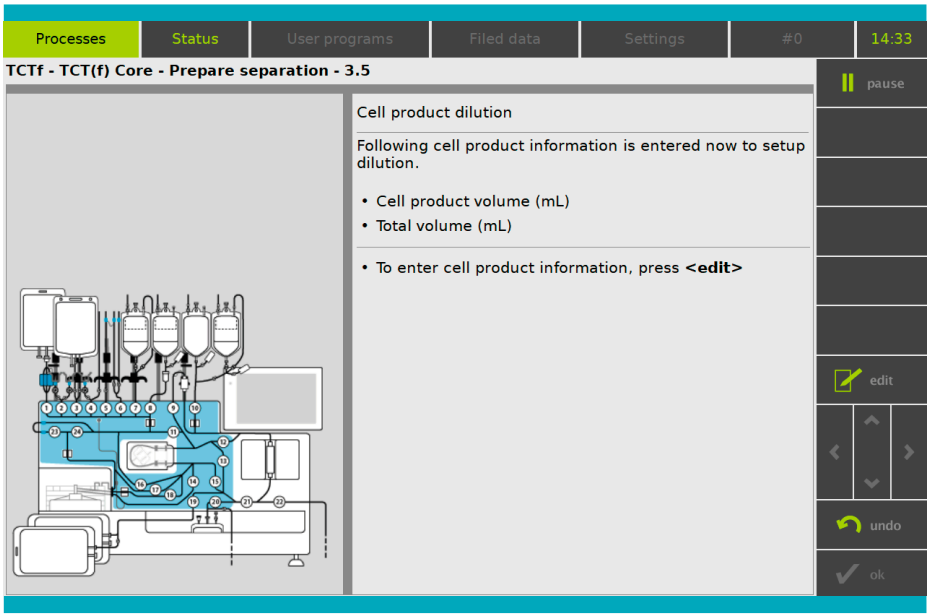
Risk of low performance or loss of cell product. Long holding times of the thawed cellular product might result in low cell viabilities and low separation performance.

- Do not thaw the frozen leukapheresis until instructed to do so.

⚠ CAUTION

Risk of cell loss. Depending on the leukapheresis freezing protocol, a dilution with medium can lead to clumps and loss of cell product.

- Consider using process buffer for dilution. Do not thaw the frozen leukapheresis until instructed to do so.



Screen 7.40: Cell product dilution for frozen leukapheresis

An automatic dilution of the cellular product with medium or process buffer can be performed when the entered total volume is higher than the cell product volume.

IMPORTANT

For some cases a second buffer bag (1 × 3L) may be required. Some additional features are performed with buffer (e.g., determination of the adjustment factor and automated dilution of a frozen-in cell product).

Enter the frozen cell product volume (e.g., 50 mL) and the total volume (e.g., 150 mL) that shall be achieved after dilution (see Screen 7.40). The corresponding dilution volume (e.g., 100 mL) is calculated automatically.

Both, cell product volume and total volume, have to be in the range of 50 to 300 mL. Be aware that the dilution volume is limited to 150 mL.

In the next step, choose whether buffer or medium should be used for the dilution.

The dilution volume of medium or process buffer will be pumped into the Application Bag directly after the priming sequence.

IMPORTANT
Make sure that the cell product volume does not exceed 300 mL.

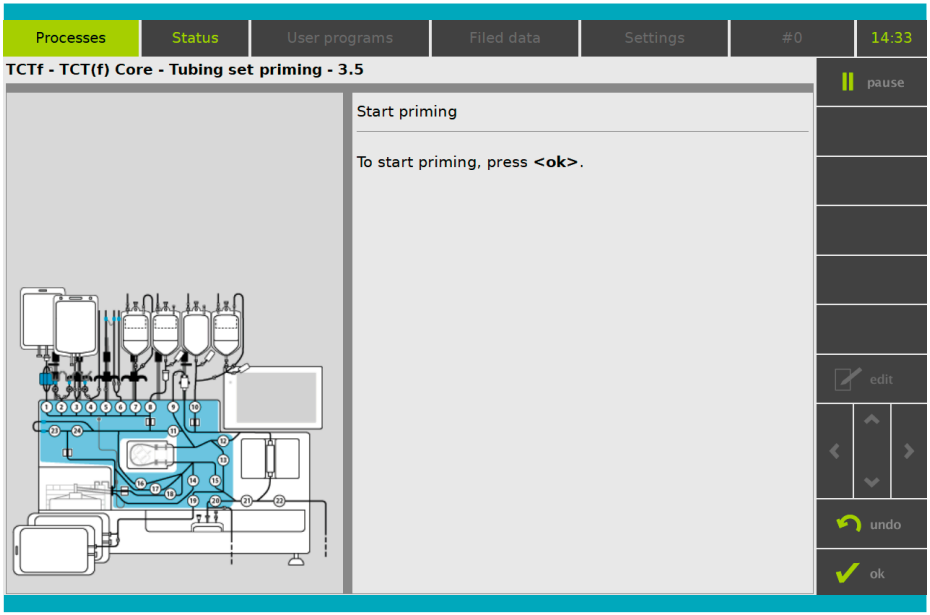
In case the cell product volume is the same as the total volume, no dilution will be performed. An orange dialog box appears to inform the user.

To confirm the entered values, tap **<ok>**. To change the entered values, tap **<edit>**. Otherwise tap **<ok>** to proceed.

Be aware that after values were entered and confirmed the process does not allow a change of previously entered values. The dilution volume that will be pumped into the Application Bag cannot be changed and might result in a wrong dilution of the thawed cell product.

IMPORTANT
The combination of a frozen leukapheresis and an enrichment of CD62L positive cells is biologically not possible, because CD62L is downregulated after thawing.

7.4.3 Priming phase

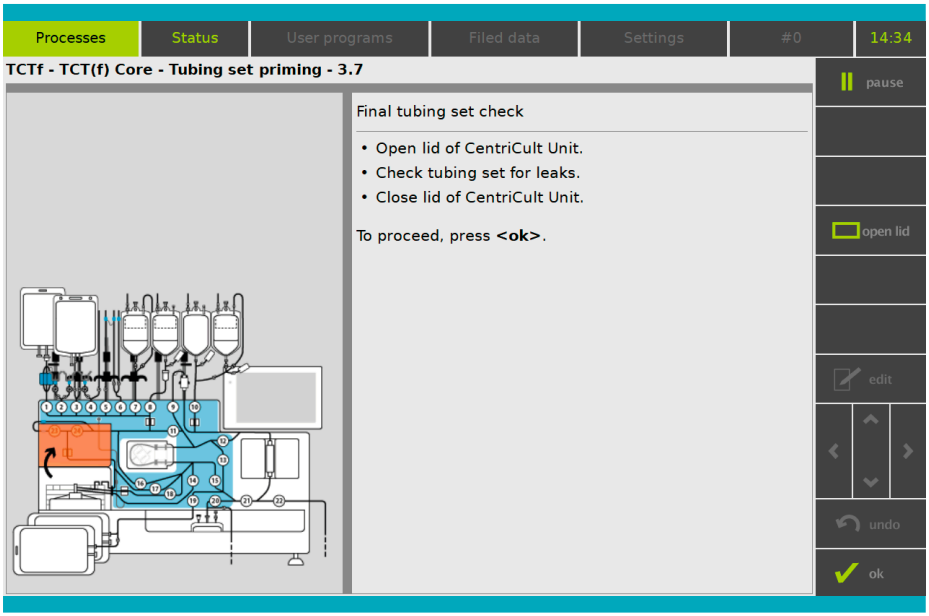


Screen 7.41: Start of priming phase

To start the priming of the tubing set, tap <ok>.

During the priming phase, the Reapplication Bag is filled with medium, and the tubing set is filled with process buffer. The pump adjustment factor for the specific process will be determined.

The time for the priming phase will be shown as a process bar on the screen.

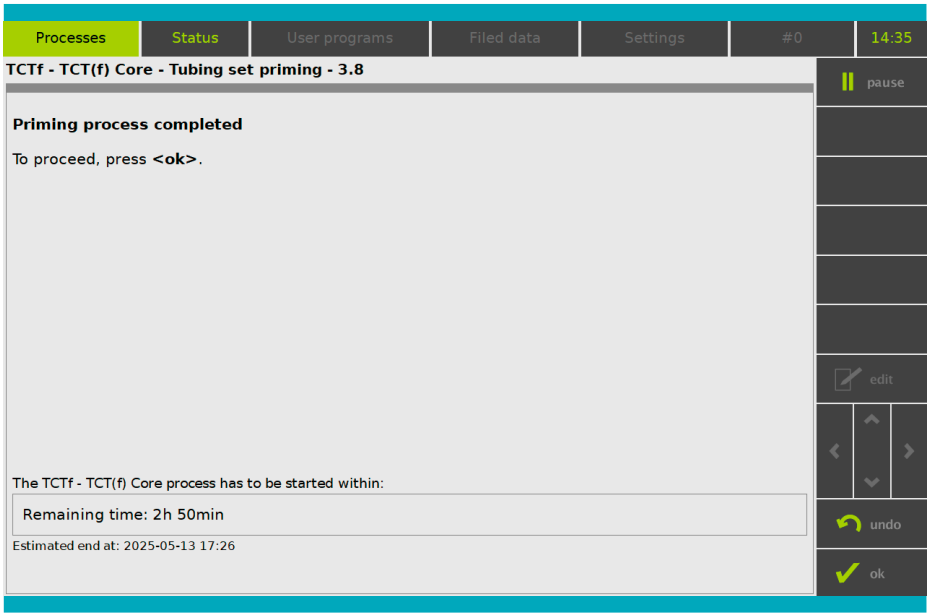


Screen 7.42: Final tubing set check after priming phase

When the priming phase is completed, check all tubing, fittings, valves, chamber, and columns for leaks or kinks that may block the fluids (see Screen 7.42). In case there is any leakage, restart the process with a new tubing set, medium, and buffer.

The CentriCult Unit lid unlocks automatically during this process step. If the lid does not unlock automatically, tap <open lid> on the toolbar (see Screen 7.42). In the event the lid cannot be opened, contact Miltenyi Biotec Technical Support.

IMORTANT
If an automated dilution of frozen cell product was chosen, make sure that medium or process buffer is provided in the Application Bag before transferring the cell product.



Screen 7.43: End of priming phase

IMPORTANT

It is recommended to perform the tubing set priming directly before the enrichment process and not more than 3 hours in advance. Make sure that the separation reagent(s) and the cellular starting product are available for the separation phase.

7.5 Preparation for the automated enrichment process

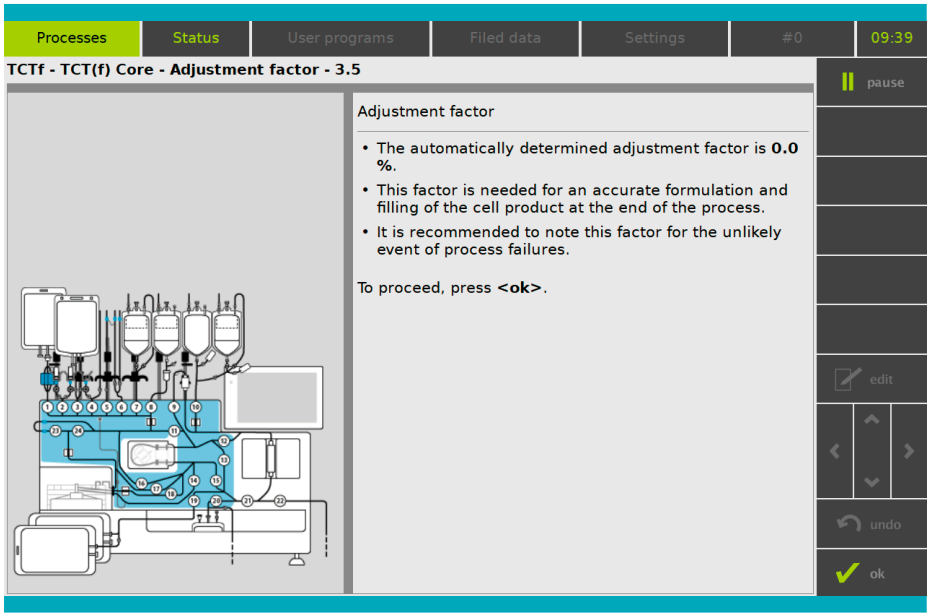
7.5.1 Adjustment factor

During the priming of the tubing set, a tubing set specific pump adjustment factor in percent is determined automatically and shown on the process screen.

⚠ CAUTION

Risk of inadequate quantity of cells or impaired potency of cells. The automatically determined adjustment factor is essential for the accurate formulation and filling of the cell product at the end of the process.

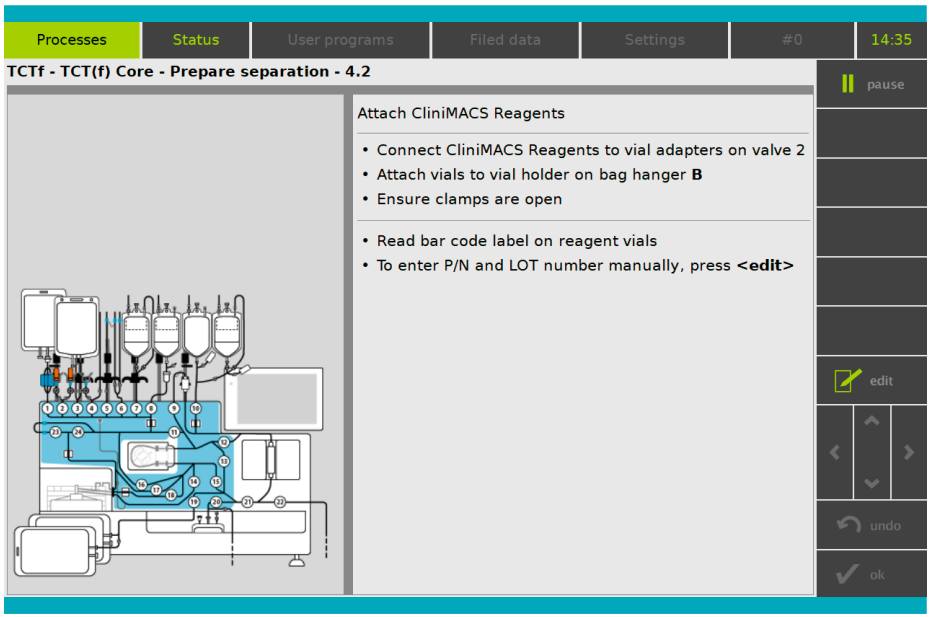
- Note down the adjustment factor value as a reference for the unlikely event of process failures.



Screen 7.44: Adjustment factor

7.5.2 Connection of CliniMACS Reagents

According to prior process selection, connect either one vial of the CliniMACS CD62L Reagent or one vial of each CliniMACS CD4 Reagent and CliniMACS CD8 Reagent to the vial adapters on valve 2.



Screen 7.45: Connection of CliniMACS Reagent

If connecting one vial of CliniMACS CD62L Reagent:

- Remove the plastic cap from the vial.
- Close one of the clamps on the vial adapters first and place this vial adapter on top of the instrument between the bag hangers.
- Turn the other vial adapter upside down.
- Carefully push the adapter into the vial while slightly turning until the spike penetrates the elastomer stopper and the adapter plastic ring snaps into place.
- Ensure that the septum is punctured, allowing free flow of liquid.
- In one smooth motion, turn the vial and vial adapter back again and insert the CliniMACS CD62L Reagent vial into the vial holder on bag hanger B. For correct connection, see Figure 7.9.
- Adjust height of the vial holder.

If connecting one vial of CliniMACS CD4 Reagent and one vial of CliniMACS CD8 Reagent:

- Remove the plastic cap from the vials.
- Turn both vial adapters upside down.
- Carefully push the adapters into the vials while slightly turning until the spikes penetrate the elastomer stoppers and the adapter plastic rings snap into place.
- Ensure that the septum of each vial is punctured, allowing free flow of liquid.
- In one smooth motion, turn the vials upside down and insert both CliniMACS Reagent vials into the vial holder on bag hanger B. For correct connection, see Figure 7.12.
- Adjust height of the vial holder.

Read the barcode label on the vial(s) or tap **<edit>** to enter part number(s) (P/N) and lot number(s) (LOT) manually with the keyboard shown on the screen (see Screen 7.45).

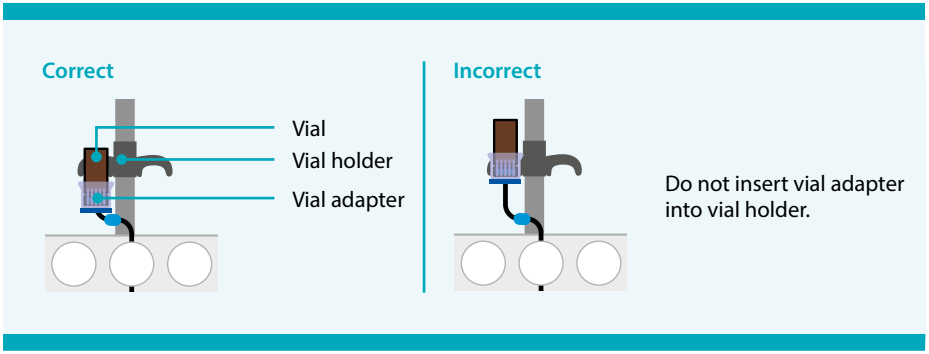


Figure 7.12: Connection of vials to vial holder

7.5.3 Prepare cell separation

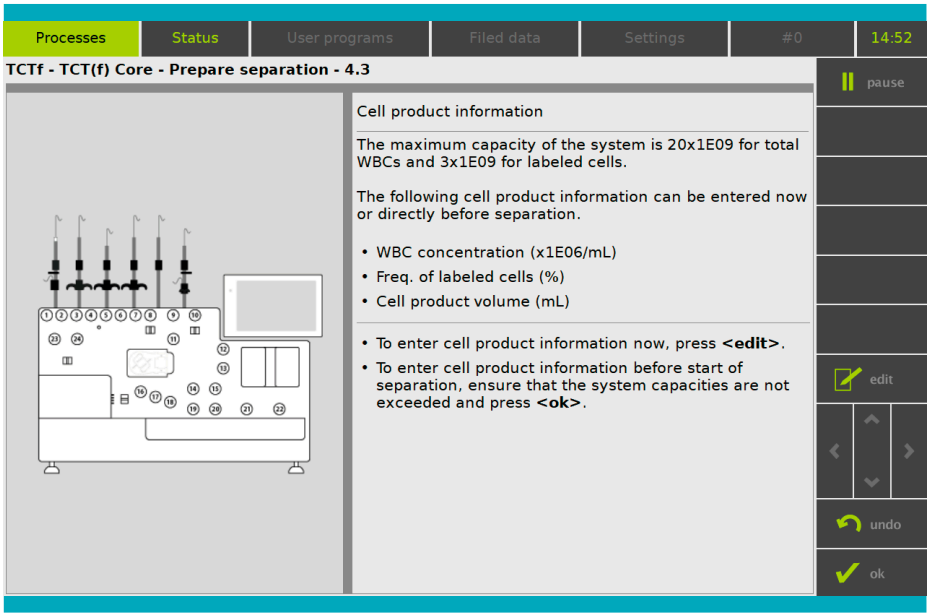
Preparation of fresh cell product

Before connecting the cell product bag to the tubing set, determine the volume, the WBC concentration and the frequency of cells to be labelled.

IMPORTANT

If the total number of cells to be labelled is higher than 3×10^9 cells, the process capacity is exceeded, and target cells will be lost in the negative fraction and will end up in the Non-Target Cell Bag. The probability of clogging might also be increased.

For details regarding how to calculate the number of target cells see section 6.1 ´Testing of cell product´.



Screen 7.46: Entry of fresh cell product information

To enter the information of the cell product, tap <edit>.

Enter the WBC concentration ($\times 10^6$/mL), the frequency of labeled cells (i.e., percentage (%) of CD4/CD8 positive cells or percentage (%) of CD62L positive cells) and the volume of the cell product that will be transferred to the Application Bag (see section 6.1 ´Testing of cell product´).

Optionally, tap <ok> to enter the parameters later during the process. If choosing to continue without parameter input at this time, the input will have to be done in the middle of the automatic enrichment process, specifically right before the cells are loaded onto the column. This requires user interaction before the enrichment process continues.

IMPORTANT
In case it is chosen to enter the parameter at a later time point during the process, ensure that the number of labeled cell do not exceed the column capacity.

Preparation of frozen cell product

⚠ CAUTION

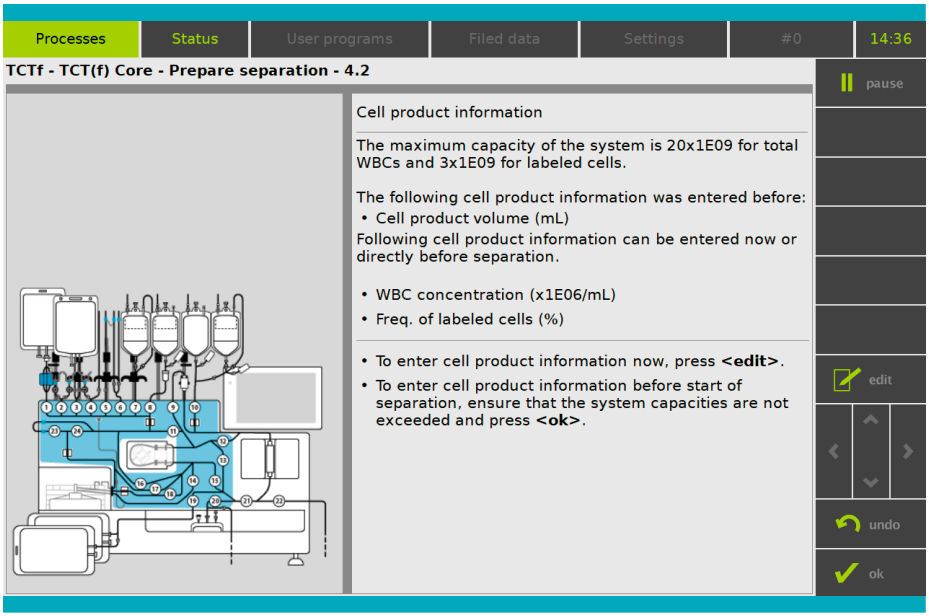
Risk of low performance or loss of cell product. Long holding times of the thawed cellular product might result in low cell viabilities and low separation performance.

- Do not thaw the frozen leukapheresis until instructed to do so.

⚠ CAUTION

Risk of tubing set damage. Dimethyl sulfoxide (DMSO) concentrations higher than 20 % (v/v) (22% (w/v)) with longer exposure times than 24 hours and temperatures above room temperature are not recommended for the tubing set.

- If solutions with higher DMSO concentration should be connected to the tubing set, it is recommended to dilute the solution in advance.



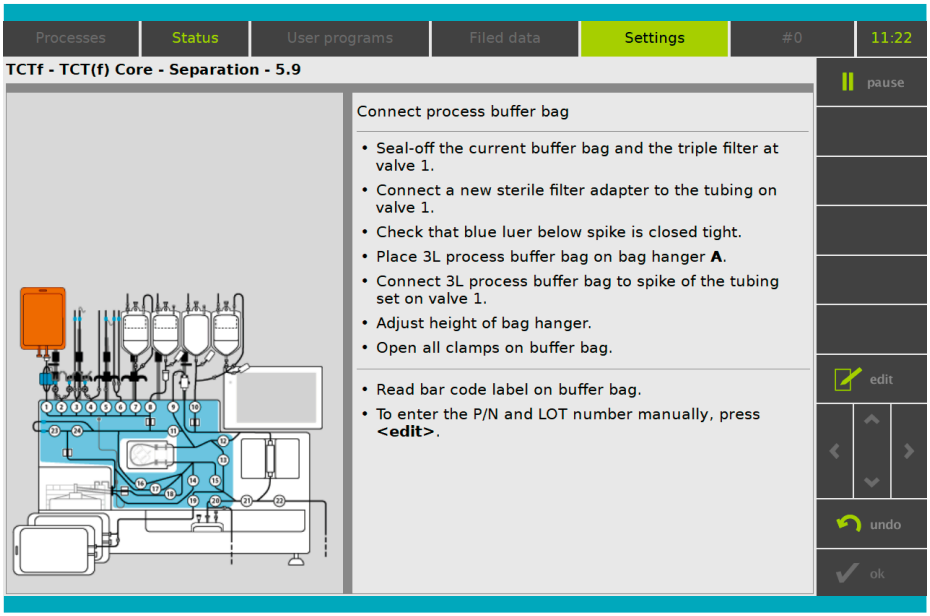
Screen 7.47: Entry of frozen cell product information

To enter the information of the cell product, tap <edit>.

Enter the WBC concentration ($\times 10^6$/mL), the frequency of labeled cells (i.e., percentage (%) CD4/CD8 positive cells or percentage (%) CD62L positive cells) (see Screen 7.41).

Be aware to enter the parameters referring to the original frozen cell product volume and concentration. When a sample has been taken from the Application Bag, consider the potential dilution with dilution volume of medium or buffer.

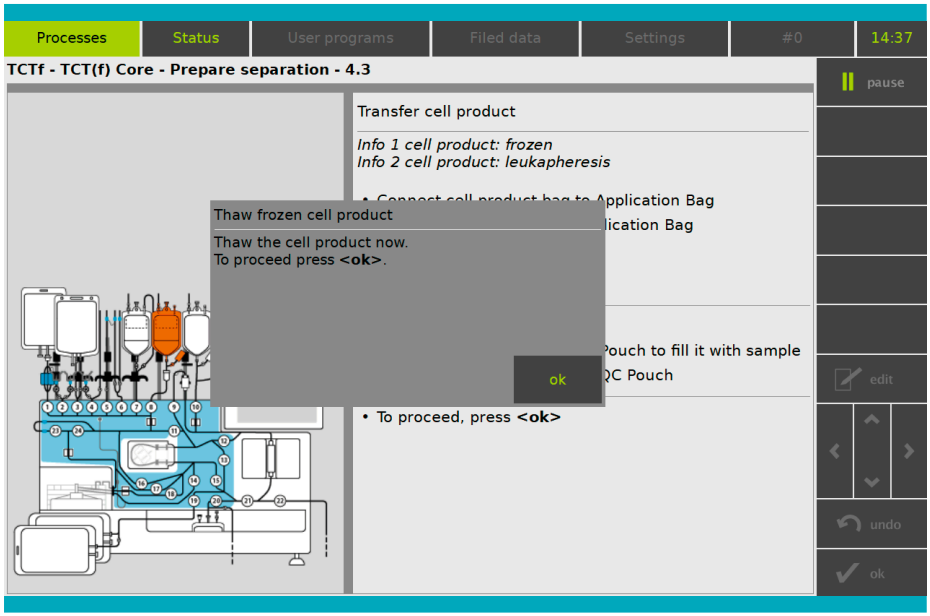
In a special case, when the frozen leukapheresis was diluted with process buffer and the number of labelled cells exceeds 2×10^9 cells, the process will perform three enrichment stages and 3L of process buffer are not sufficient. The process will show a warning and instructions to replace the connected process buffer bag with a new 3L bag (see Screen 7.48).



Screen 7.48: Connection of new process buffer

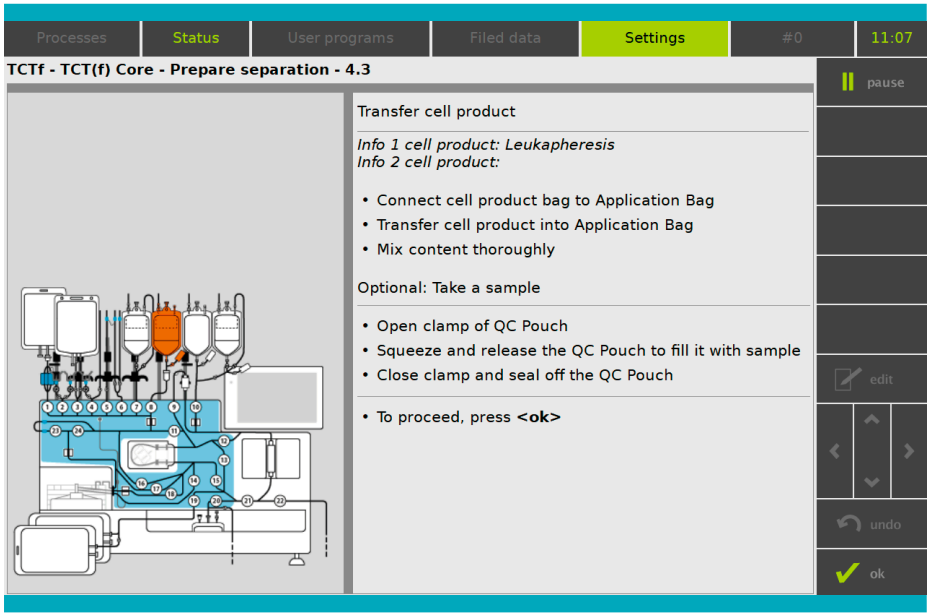
Optionally, tap <ok> to enter the parameters later during the process. If choosing to continue without parameter input at this time, the input will have to be done in the middle of the automatic enrichment process, specifically right before the cells are loaded onto the column. This will require user interaction before the enrichment process continues.

The process will show instructions to thaw the frozen cell product now (see Screen 7.49).



Screen 7.49: Thawing of frozen cell product

Transfer of cell product



Screen 7.50: Transfer of cell product

To transfer the cell product to the Application Bag, follow the institution's standard operating procedures. For example, connect a 1m tube extension with a luer to the spike connector and spike it into the spike port of the cell product bag.

Then connect the cell product bag to the Application Bag via sterile welding. Transfer the cell product into the Application Bag and seal off the empty bag using a heat sealer. Make sure to gently mix the Application Bag after transfer to ensure homogeneous dilution of the cell product.

Taking a sample from the Application Bag

IMPORTANT
For WBC concentration values, which are obtained from the thawed and diluted cell product drawn from the Application Bag, always consider the dilution factor.

To take a sample from the blood product:

- Open the clamp of the QC Pouch
- Squeeze and release the pouch once to fill the QC Pouch with cellular starting product.
- Multiple squeezes and releases will increase the sample volume in the QC Pouch. The maximum volume capacity of the QC Pouch is 4 mL.
- Close the clamp and seal off the QC Pouch.

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

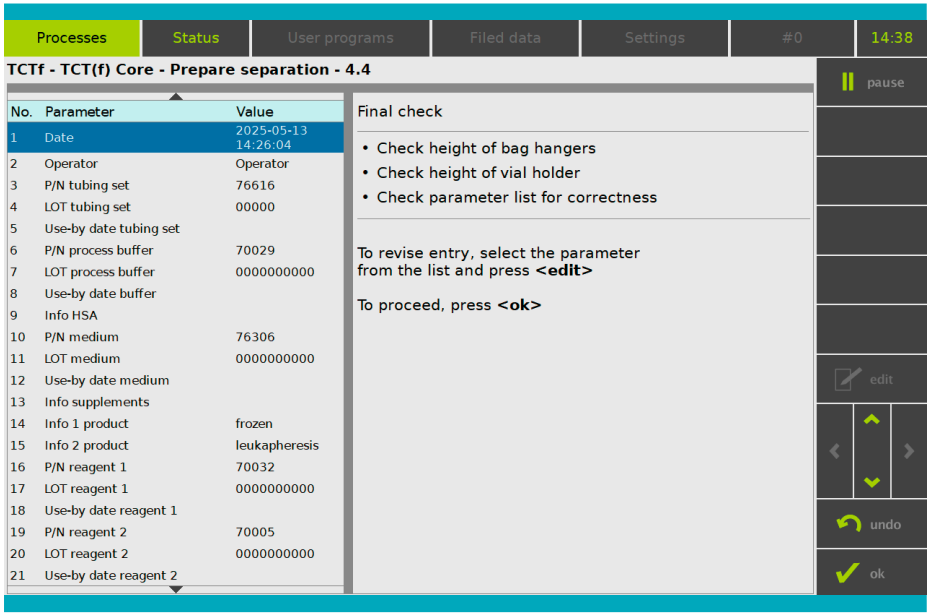
To enter information regarding the cell product, tap **<edit>** .

⚠ CAUTION

Risk of low separation performance. The application software calculates the separation stages with the original cell product volume and concentration.

- If the sample is taken from the diluted cell product in the Application Bag, consider the dilution factor during parameter entry.

7.5.4 Final check



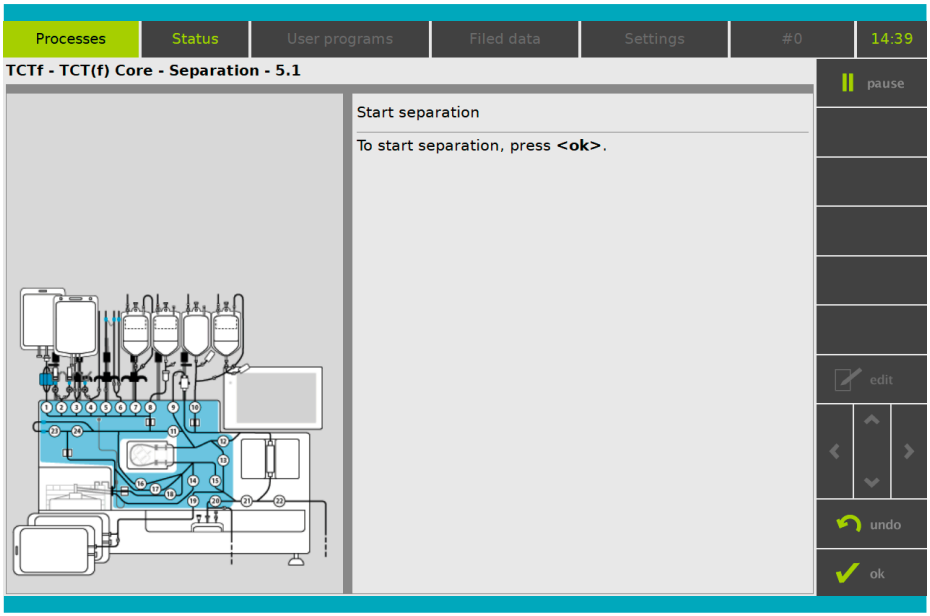
Screen 7.51: Final set-up check

Parameters can only be revised but not edited at this point. To return to the previous screen, tap <undo> (see Screen 7.49).

At this time all pre-handling steps for the enrichment part of the T Cell Transduction and Automated Formulation System are complete, and the automated enrichment process can begin.

7.6 Automated enrichment process

7.6.1 Start of enrichment process



Screen 7.52: Start of automated enrichment process

To start the enrichment, tap <ok> (see Screen 7.52). A pop-up window will appear.

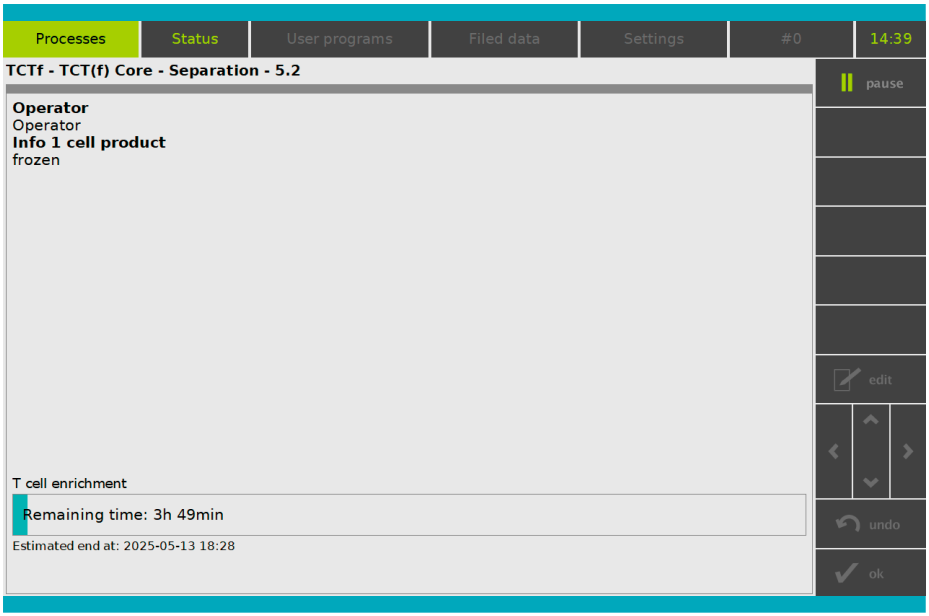
To confirm the start of the enrichment process, tap <yes>.

If the parameter entry was skipped, another promt to enter the cell product information will be shown before the magnetic separation. The requested parameters volume and cell concentration refer to the original undiluted cell product.

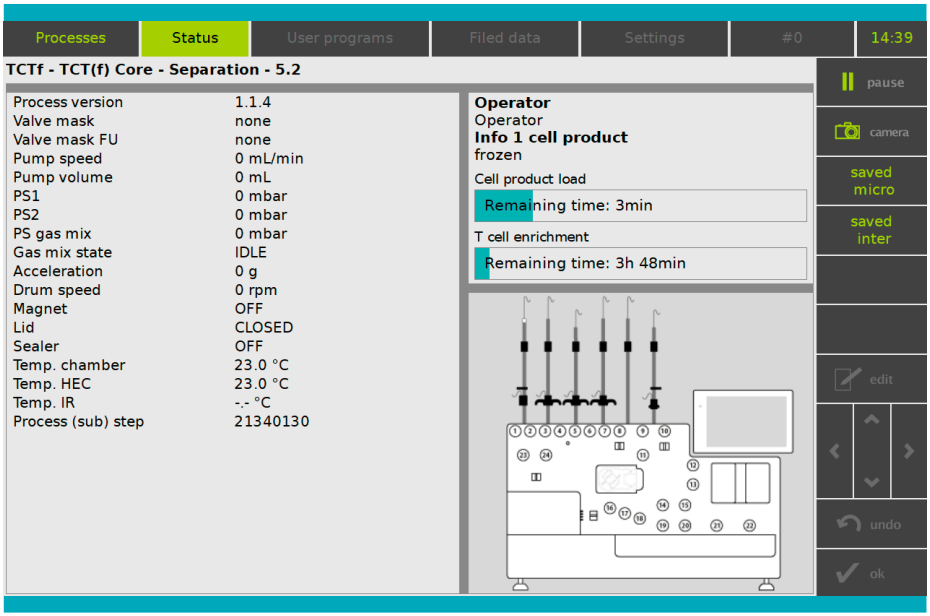
The fully automated enrichment process is divided into several phases:

1. Sample loading
2. Red blood cell reduction if necessary
3. Washing/volume adjustment
4. Labeling
5. Removal of excess reagent
6. Cell filtration
7. Magnetic separation
8. Elution

To monitor the different phases during the process, tap <Status> on the menu bar. For details, refer to CliniMACS Prodigy User Manual (Instrument).



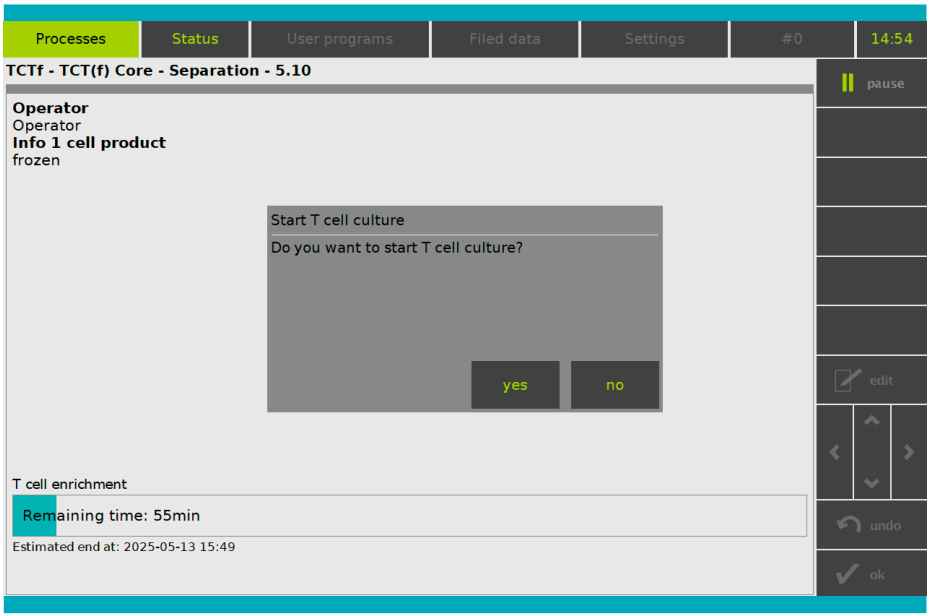
Screen 7.53: Generic information screen (Processes)



Screen 7.54: Generic status screen displaying real-time process info (Status)

7.6.2 Completion of enrichment process

After the enrichment process, a pop-up window will ask if the process should be continued with cultivation.



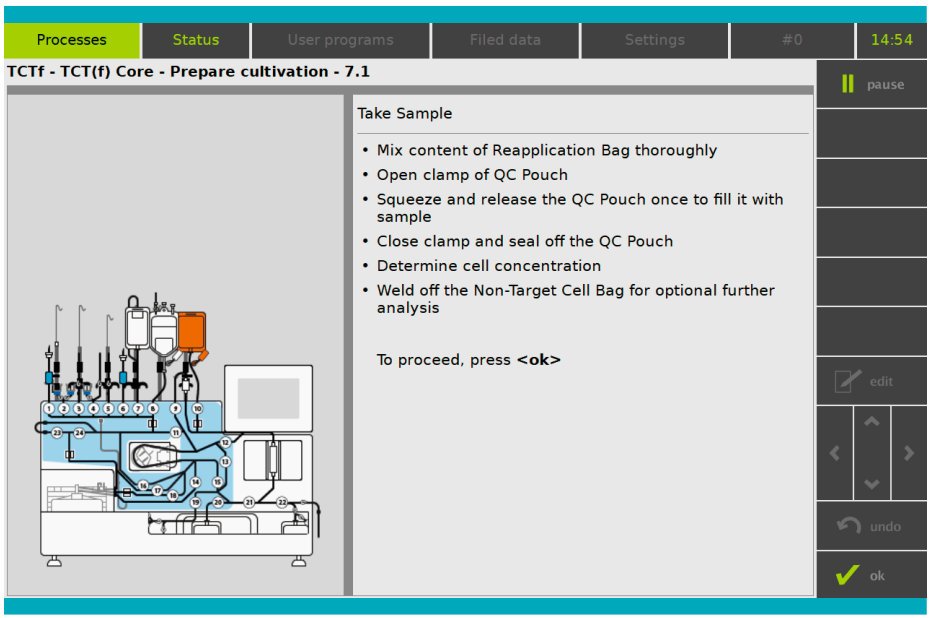
Screen 7.55: Pop-up with start of T cell culture

To perform cultivation, tap <yes> and proceed with the analysis of the target cell fraction (see section 7.6.3 ´Analysis of enriched target cell fraction´).

If no cultivation is required, tap <no> and proceed to final handling (see section 8.5 ´Final handling´ on page 145).

The Reapplication Bag above valve 10 contains the enriched target cell fraction. Seal off the Reapplication Bag to retrieve the enriched cells.

7.6.3 Analysis of enriched target cell fraction



Screen 7.56: Taking a sample from target cell fraction

To take a sample of the enriched target cell fraction from the Reapplication Bag:

- Mix the content of the Reapplication Bag thoroughly.
- Open the clamp of the QC Pouch.
- Squeeze and release the pouch once to fill the QC Pouch with cellular starting product.
- Multiple squeezes and releases will increase the sample volume in the QC Pouch. The maximum volume capacity of the QC Pouch is 4 mL.
- Close the clamp at the top end of the tubing and seal off the tubing.

Store all QC samples at +4 to +8 °C (+39 to +46 °F).

Analyze QC samples according to the institution's standard operating procedure.

⚠ 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.

IMPORTANT

To avoid sample loss, seal off the Non-Target Cell Bag close to the tube branch leading to the Formulation Unit. Do not seal off the tube to the formulation valve.

8

Cultivation of T cells

8.1 General remarks

⚠ WARNING

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

- Connect all bags and vials by sterile welding.
- Perform all preparative steps in a sterile environment (e.g., laminar flow hood) using aseptic techniques.

IMPORTANT

During the entire cultivation process the following must be considered:

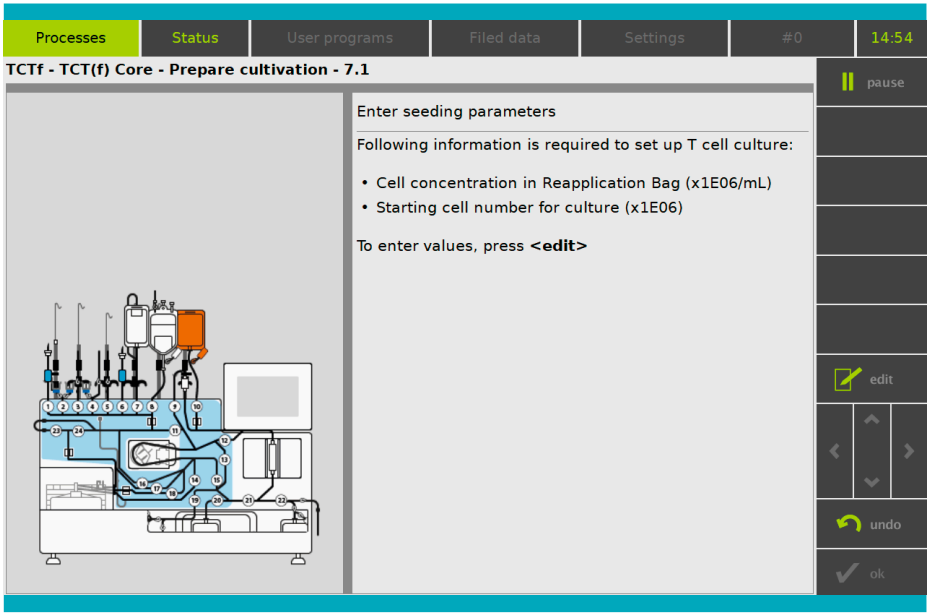
Every 10 hours, the tubing set is rinsed with 10 mL of medium connected to valve 3. Therefore, sufficient medium must always be connected to the tubing on valve 3 (e.g., if the instrument is running for 72 hours without set activities, a minimum of 80 mL medium must be connected).

Each Waste Bag connected to the tubing set has a capacity of 5 liters. If a long process with many feeding and/or washing steps is to be performed, regularly check that the Waste Bag is not overfilled.

8.2 Preparation for the cultivation

This section guides step by step through the setup of the cultivation part of the T Cell Transduction and Automated Formulation process. Each screen shows the instructions supported by a picture. At any step during the setup tap <undo> to return to a previous step.

8.2.1 Input of cell seeding parameters



Screen 8.1: Input of seeding parameters

Enter the cell concentration of the enriched cell fraction in the Reapplication Bag determined in section 7.6.3 ´Analysis of enriched target cell fraction´ and the total number of cells to be seeded.

It is recommended to seed a total cell number of 100×10^6. This corresponds to an approximate cell seeding density of 1×10^6 cells per cm^2.

The volume to be transferred is automatically calculated.

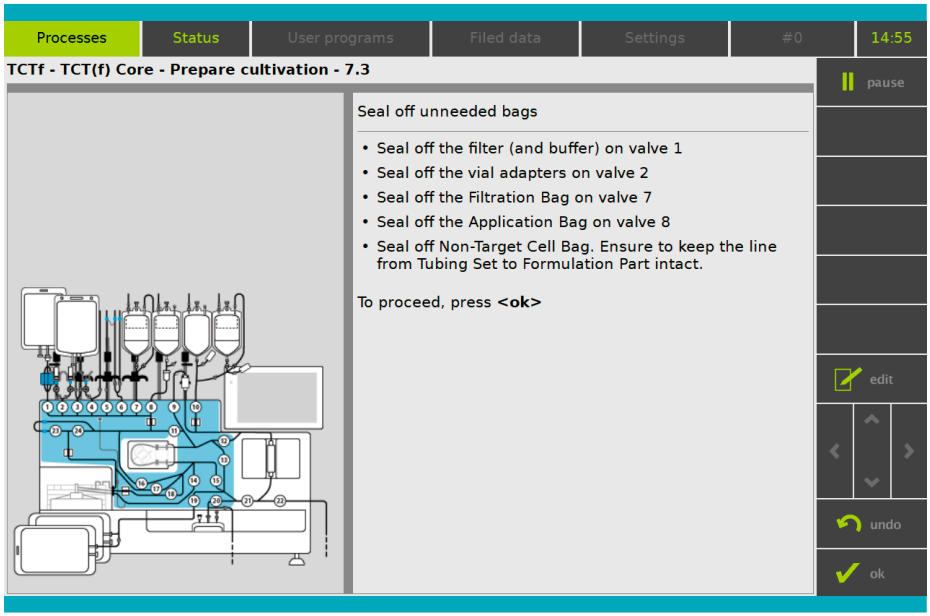
To retrieve the remaining enriched target cells (e.g., to be frozen as backup) seal off the Reapplication Bag after the automatic setup of cultivation is completed (see 8.2.6 ´Automated culture setup´). Make sure not to seal off the Filtration Bag 2.

8.2.2 Sealing off non-needed equipment

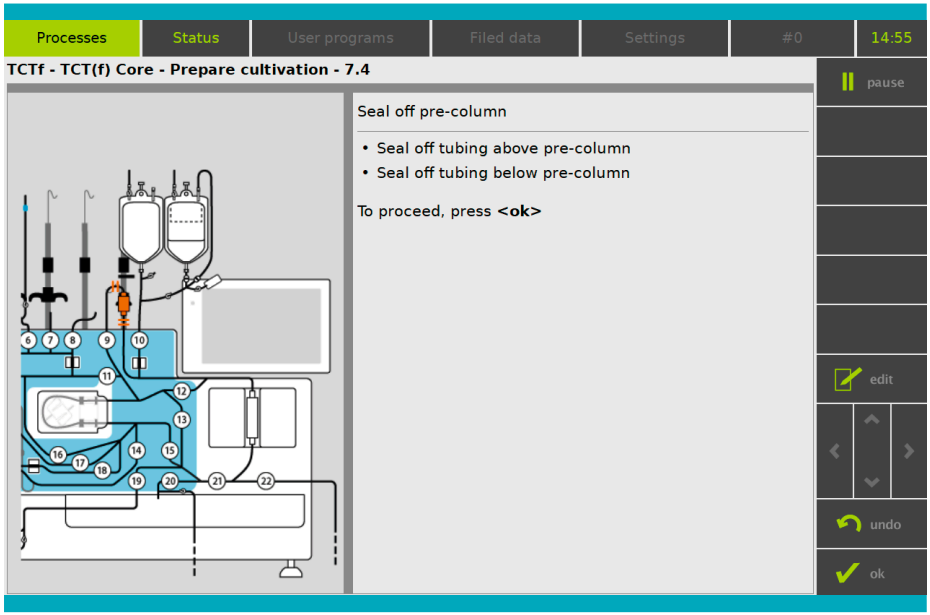
To avoid diffusion of solutions or cells from unneeded equipment during the cultivation step, seal off or clamp off the following items:

- Bags on valve 1, valve 7, and valve 8,
- Vial adapters on valve 2,
- Pre-column and the separation column of the tubing set

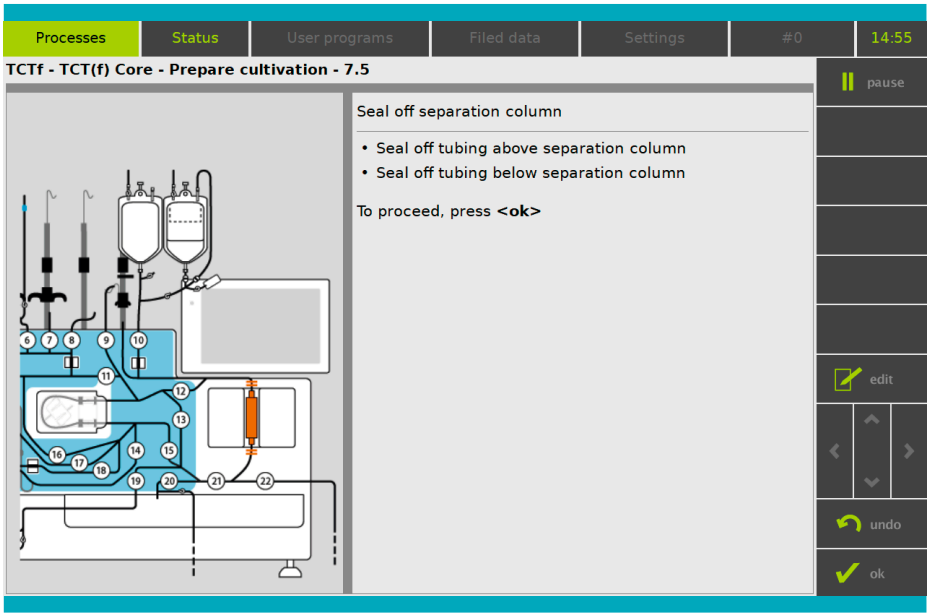
Seal off or clamp off the items as shown on Screen 8.2 to Screen 8.4.



Screen 8.2: Sealing off non-needed bags and vial adapters on valve 1, 2, 7, and 8



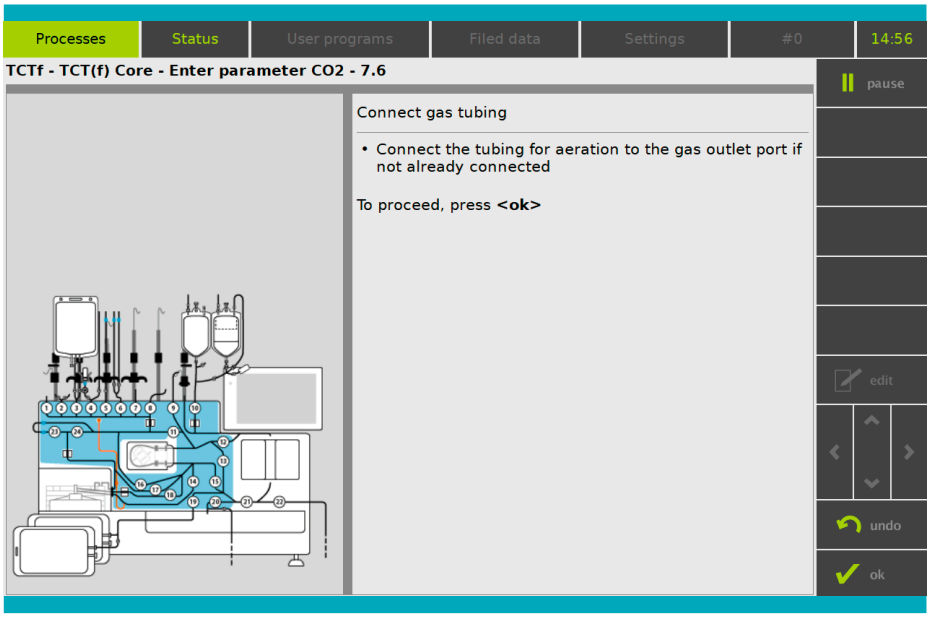
Screen 8.3: Sealing off the pre-column



Screen 8.4: Sealing off the separation column

8.2.3 Input of CO_2 and temperature parameters

If running the full process (case 1), the gas tubing has already been connected (see section 7.3.2 ´Installation steps´), tap <ok> to proceed.

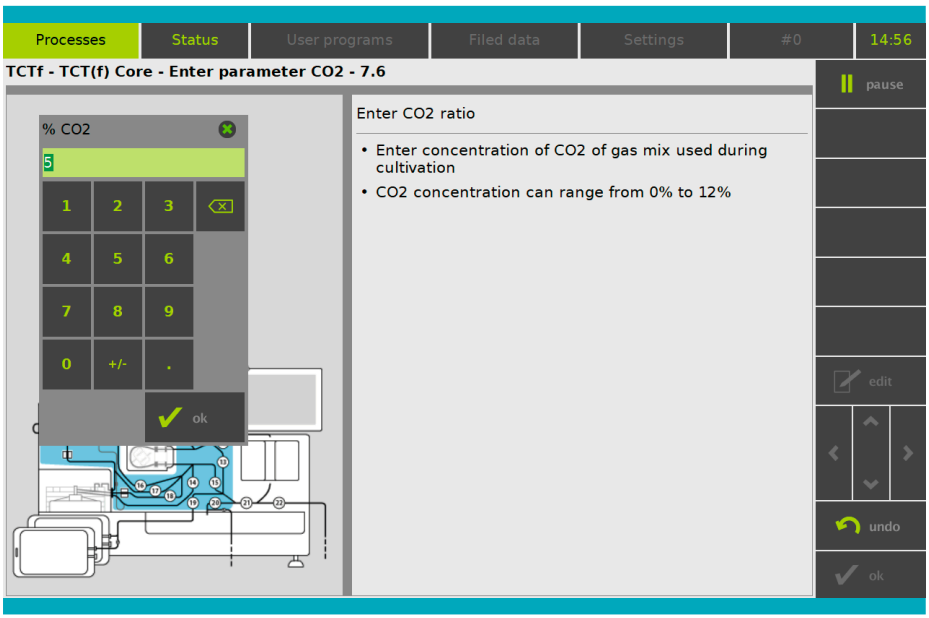


Screen 8.5: Connection of gas tubing

For the cultivation of the cells, the values for CO_2 concentration must be entered. For TexMACS GMP Medium enter 5% CO_2 (see Screen 8.6).

IMPORTANT

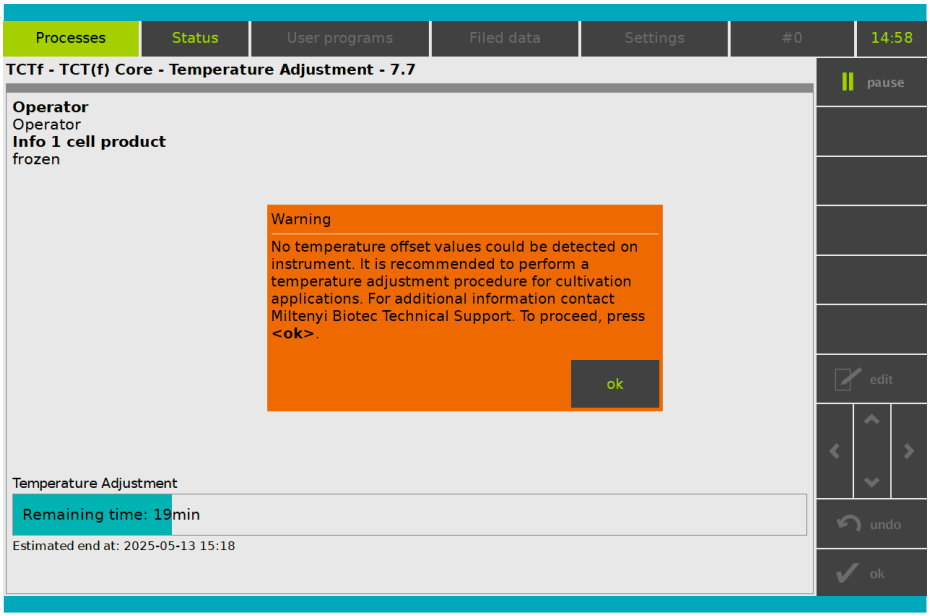
Connect the gas tube tightly to the gas outlet port to ensure proper aeration of the cells.



Screen 8.6: Input of CO_2 concentration

The temperature parameter will be set automatically to +37 °C (+99 °F), if temperature offset values are detected on the instrument.

If the instrument has no temperature offset values, a warning will appear stating that no temperature offset values could be detected on the instrument (see Screen 8.7). In this case the temperature parameter will be set automatically to +39 °C (+102 °F), which equals a cultivation temperature of +37 °C (+99 °F).

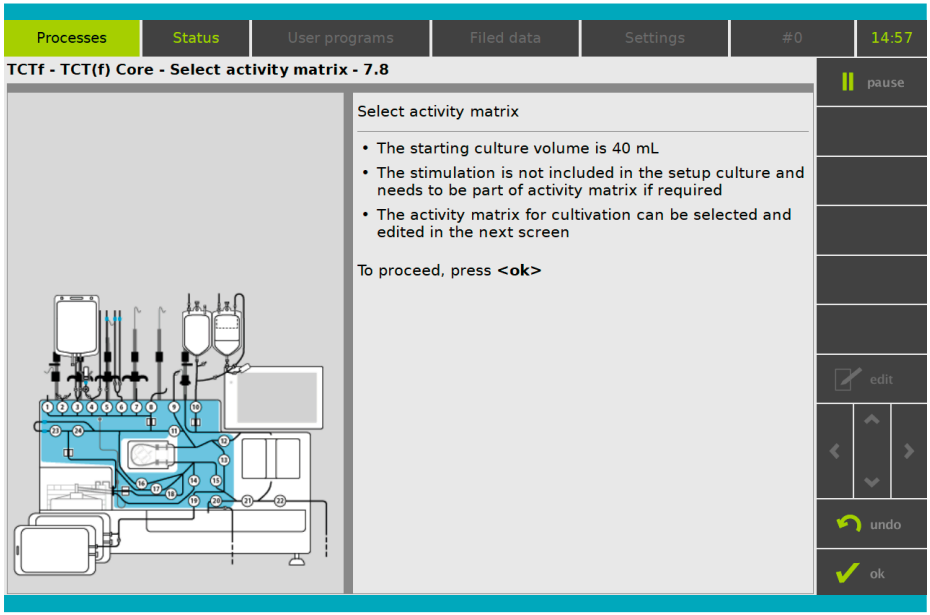


Screen 8.7: Warning which states that no offset values are detected on the instrument

IMPORTANT

It is highly recommended to receive a temperature adjustment and validation procedure for the instrument. For further information contact Miltenyi Biotec Technical Support.

8.2.4 Setup of activity matrix



Screen 8.8: Select activity matrix

The process allows customized programming of T cell cultivation steps. All T cell cultivation steps are programmed in an activity matrix.
Choose one of the following options:

- Choosing a default matrix (see ´Set default matrix´)
- Create an individual activity matrix on the CliniMACS Prodigy.

Individually designed activity matrices can be saved, imported and exported across CliniMACS Prodigy instruments (see ´Creation of individual protocols´). Each activity matrix can be modified during the cultivation phase, but those changes cannot be saved for further processes.

IMPORTANT
All steps programmed in the activity matrix are performed after the automated culture setup. The culture setup is performed automatically in one step (see section 8.2.6 ´Automated culture setup´) and is not part of the activity matrix. The automated culture setup cannot be modified.

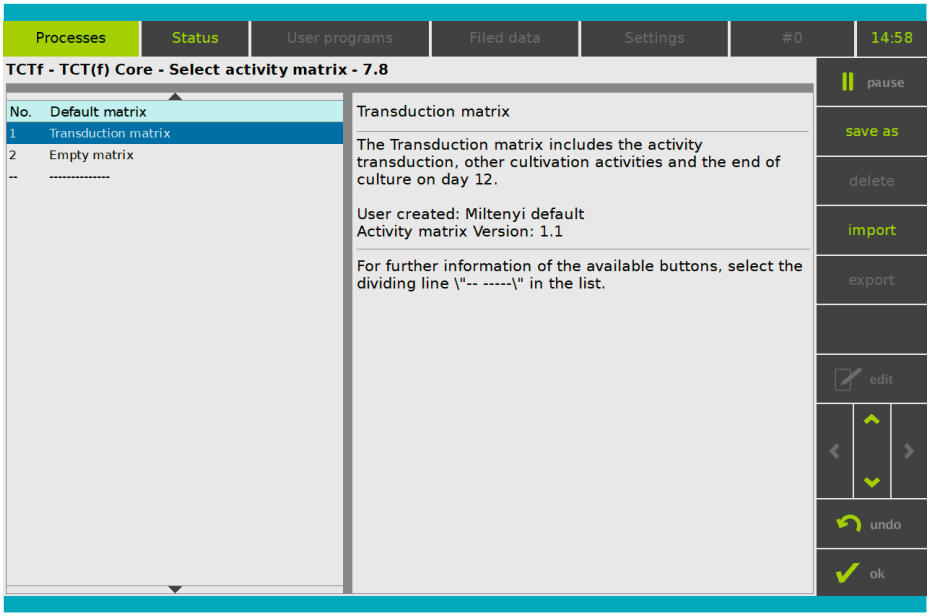
The starting culture volume after the culture setup is always 40 mL and cannot be changed.

The following activities (listed in section ´Modification of activities´) have an influence on the volume in the chamber. This volume is theoretically calculated in the activity matrix in the column "Volume" (see Screen 8.10).

The total volume in the chamber should be maintained between 70 mL and 250 mL. If these values are exceeded during the setup of the activity matrix a warning will be shown at the final confirmation step.

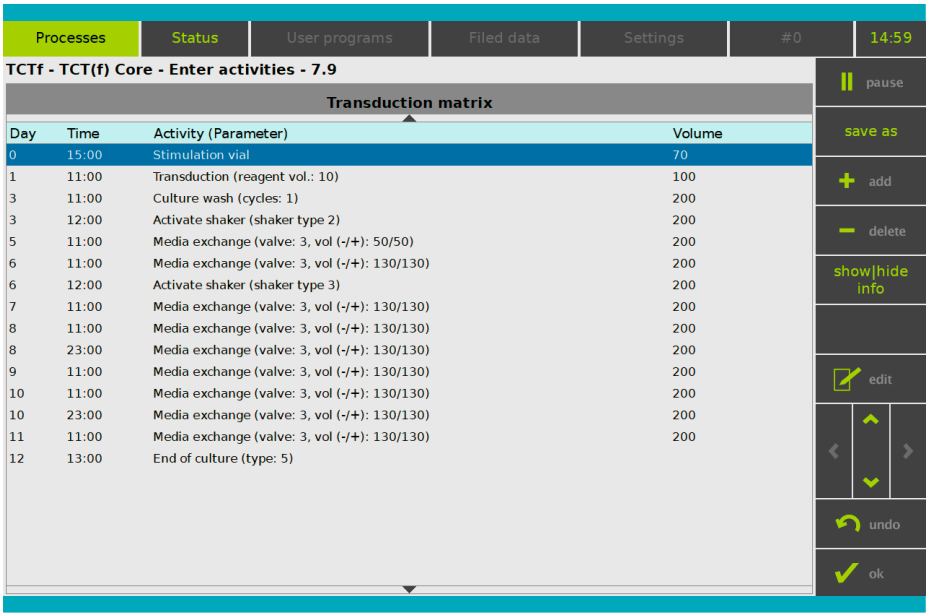
IMPORTANT
In the T Cell Transduction and Automated Formulation process the stimulation of T cells is not part of the culture setup and must be programmed into the activity matrix if required.
The T Cell Transduction and Automated Formulation System is only verified for a cultivation time of 12 days.
If the stimulation activity is skipped, the culture volume can be too low. Use the activity "Feed" to add culture medium.

Set default matrix



Screen 8.9: Set default matrix

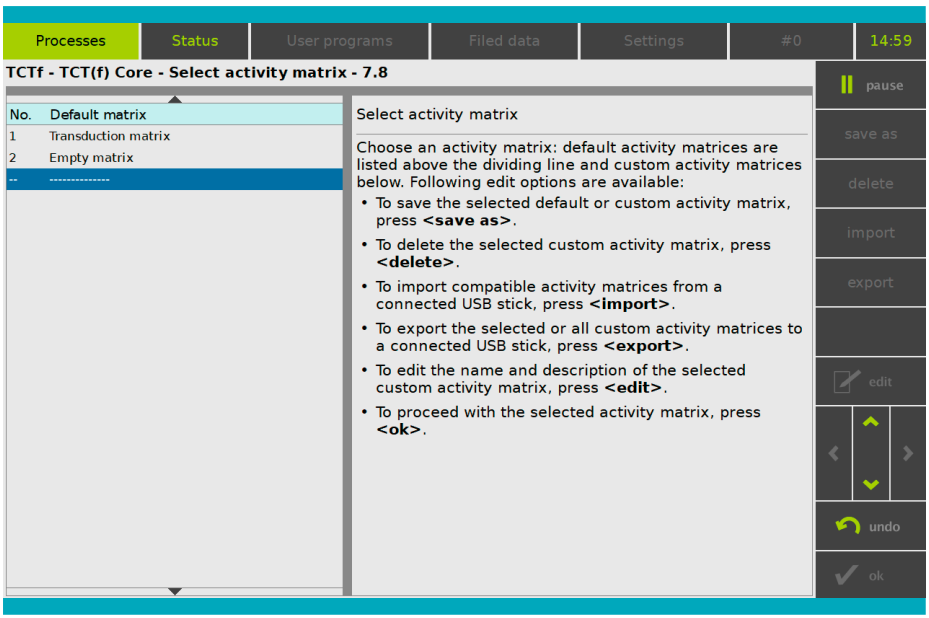
To set a default matrix tap on the matrix name in the "Default matrix" column and tap <ok>. The matrix will open and show at which day and time an activity will be performed (see Screen 8.10).



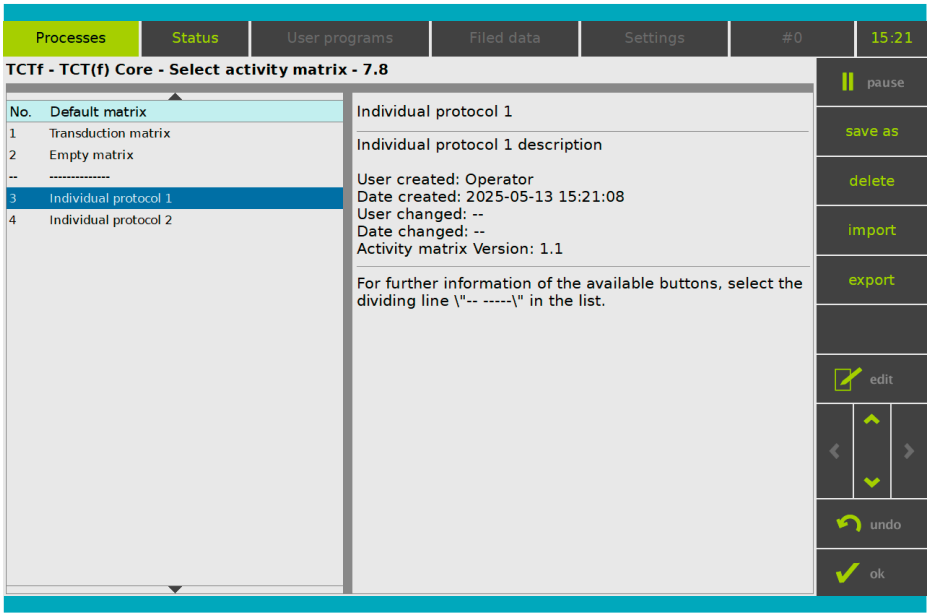
Screen 8.10: Default activity matrix – Transduction matrix

Tap <show/hide info> to show extra information on the entered parameters and instructions to edit the activity matrix.

Creation of individual protocols



Screen 8.11: Creation of individual designed activity matrices



Screen 8.12: Creation of individual designed activity matrices

The user can create individual activity matrices which can be saved on the instrument. For detailed instructions tap the dividing line (<-- ---------->) in the list on the left-hand side of the screen (see Screen 8.11).

To create an individual activity matrix, select a default matrix as a template ("Transduction matrix" or "Empty matrix") and tap **<save as>**. Rename the new activity matrix with maximal 30 digits (e.g., "Individual protocol 1") and give it an individual description with maximal 300 digits. Special characters are not allowed.

To edit an existing activity matrix, select it from the list and tap **<ok>** to open the matrix, then tap **<edit>** (see Screen 8.12).

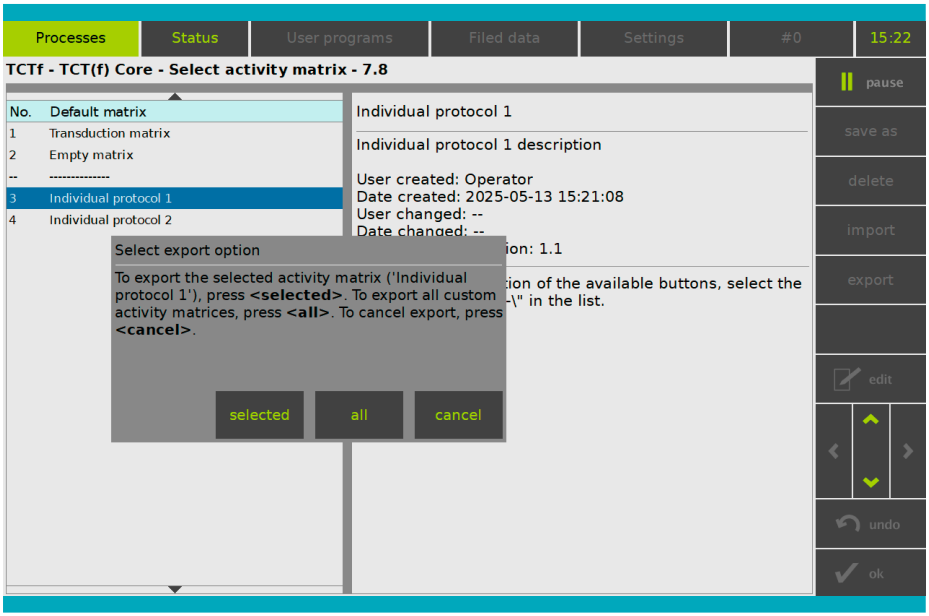
Including the two default matrices up to 50 activity matrices can be saved on the CliniMACS Prodigy concurrently. The protocols are serially numbered in the list.

The username and the current date will be logged under the description on the right side. To edit or delete newly created activity matrices tap **<edit>** or **<delete>**.

IMPORTANT

Do not use the numbering of the matrix as an identifier as the numbering can change if matrices are deleted out of the list.

Changes to the activity matrix which are made during culture will only be effective for the current run.



Screen 8.13: Export of individual designed activity matrices

Individual activity matrices can be exported and imported to further CliniMACS Prodigy instruments. For this a USB flash drive is required. It is only possible to transfer the selected or all individual activity matrices.

IMPORTANT

To use the export and import function, make sure the same application software versions are installed on the instruments.

Modification of activities

Activities	Describe	Remark
Activate shaker	Start a continuous shaking of the chamber for suspension culture	Continuous in background
Culture wash	Wash of culture to remove the stimulation reagent and/or viral vector	Automatic execution
Deactivate shaker	Switch off a previously activated shaker	Automatic execution

Activities	Describe	Remark
End of culture	**Type 1:** Cells will be rebuffered in formulation solution and transferred to Filtration Bag 2 in a final volume of 100 mL **Type 2:** Cells will be transferred to the Filtration Bag 2 with an optional fill-up with medium to max. 900 mL **Type 3:** Cells will be rebuffered in formulation solution and stored in the chamber in a final volume of 100 mL at 8°C with slow shaking **Type 4:** Cells will be stored in the chamber in the current culture volume at 8 °C with slow shaking **Type 5:** This activity enables the downstream processing of cells e.g., formulation and filling of the cell product with the Formulation Unit	User confirmation/ interaction upon execution required
Feed	Add fresh medium	Automatic execution
Media exchange	Remove old medium and add fresh medium	Automatic execution
Medium bag exchange	Prompt and user guidance to exchange medium bag	User confirmation/ interaction upon execution required
Partial harvest	Removal of cell suspension and adding of new medium to dilute the cell concentration/density	User confirmation/ interaction upon execution required
Sampling	Prompt and user guidance to take a programmed sample	User confirmation/ interaction upon execution required
Spin	Centrifugation step to be used after addition of viral vector for spinoculation protocol	Automatic execution
Stimulation bag	Transfer of stimulation reagent to the chamber	User confirmation/ interaction upon execution required
Stimulation vial	Transfer of MACS GMP T Cell TransAct to the chamber	User confirmation/ interaction upon execution required
Temperature change	Change of cultivation temperature	Automatic execution

Activities	Describe	Remark
Transduction	Transfer of viral vector to the chamber	User confirmation/ interaction upon execution required
Volume reduction	Volume reduction of culture using centrifugation, e.g., to be used before transduction with large viral vector volumes	Automatic execution
Waste Bag exchange	Prompt and user guidance to exchange Waste Bag	User confirmation/ Interaction upon execution required

Table 8.1: Available activities for cultivation

⚠ CAUTION

Risk of cell loss. A culture volume of 200 mL has been verified. Higher culture volumes can lead to foaming and wet and blocked filters.

- It is recommended not to exceed a culture volume of 200 mL.

⚠ CAUTION

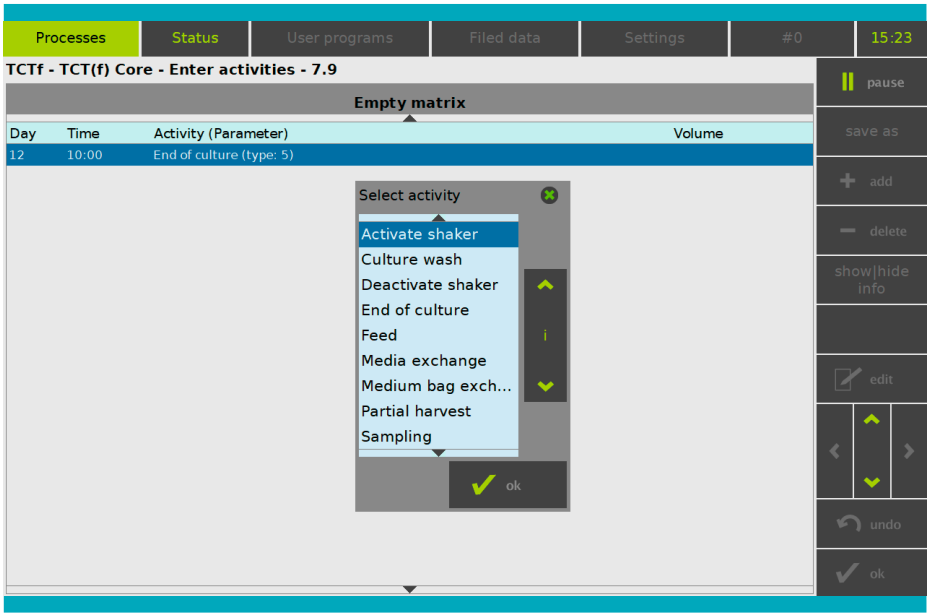
Risk of inadequate quantity of cells or impaired potency of cells. Stimulation at a inappropiate time in the activity matrix can lead to wrong dilution of MACS GMP T Cell TransAct.

- It is recommended to use the standard activity matrix.

⚠ CAUTION

Risk of inadequate quantity of cells or impaired potency of cells. If an activity requires user interaction, a pop-up will appear.

- Proceed as required to avoid interruption of gassing or temperature control.

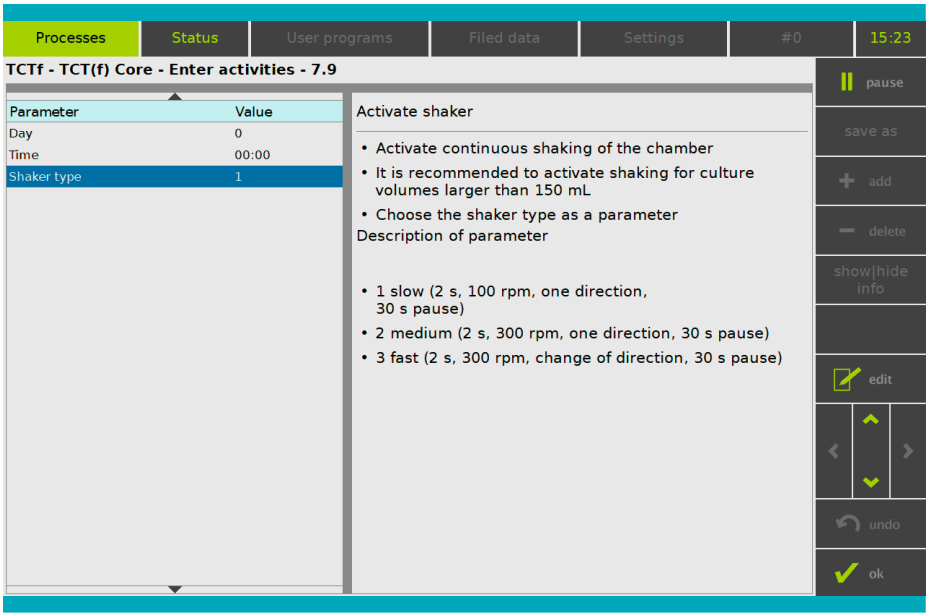


Screen 8.14: Addition of an activity

To add an activity to an opened matrix, tap <add> and select the activity from the pop-up list (see Screen 8.14). A screen specific for that activity opens.

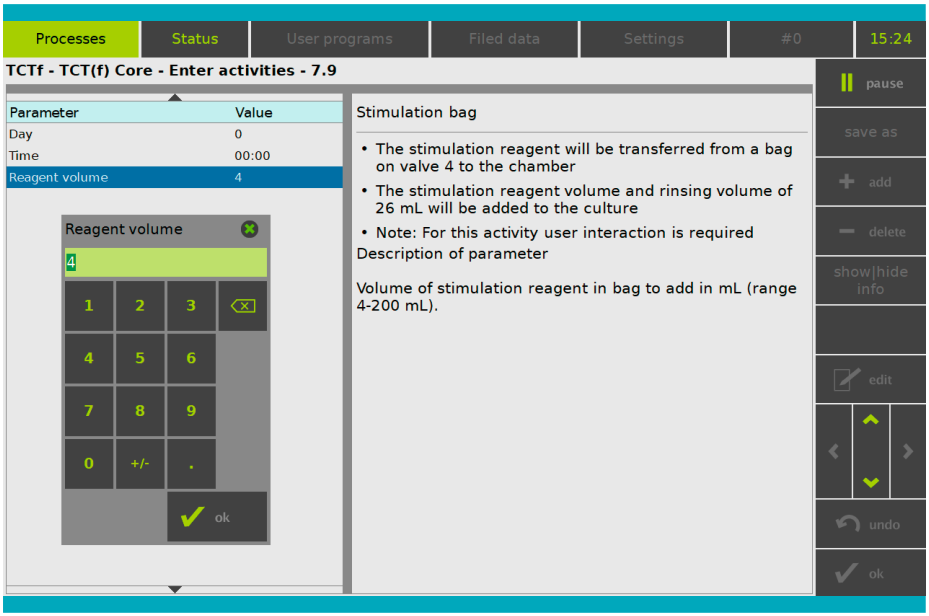
Tap <edit> to change the parameters of the activity. In general, the parameters "Day" and "Time" and additional activity specific paremeters (e.g. types or volumes) can be changed (see Screen 8.15 and Screen 8.16).

To confirm and to return to the matrix tap <ok>.



Screen 8.15: Exemplary editing of activity "Activate shaker"

Several shaker types are available for varying culture densities.



Screen 8.16: Exemplary editing of activity "Stimulation bag"

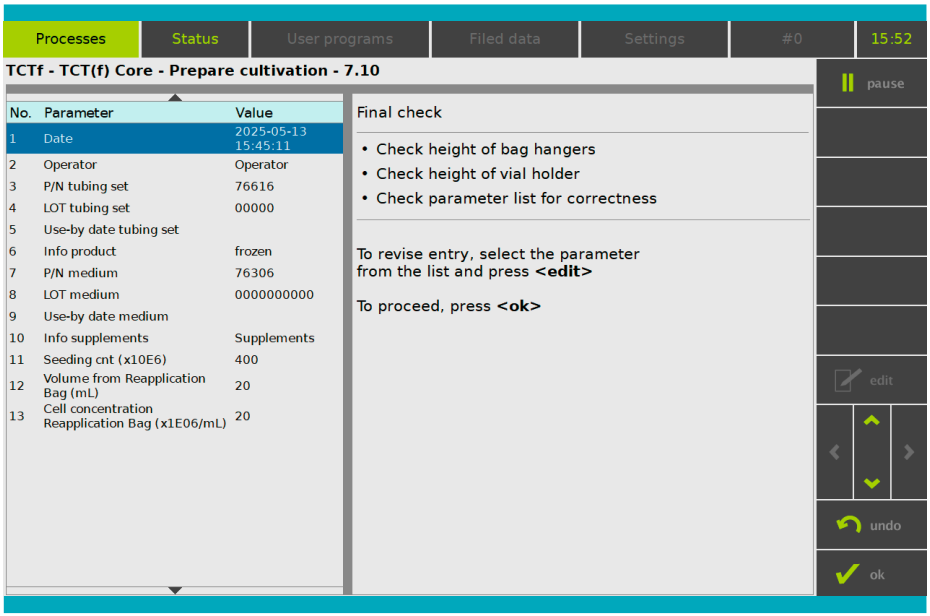
Important

When planning the process, consider that user interaction is required prior to the execution of the activities “Stimulation vial”, “Stimulation bag”, “Transduction”, “Medium bag exchange”, ”Partial harvest”, “Sampling”, “Waste Bag exchange”, and “End of culture” (see Table 8.1).

The replacement of the medium bag should be planned according to the activity matrix and the corresponding usage of medium. The exchange of one Waste Bag should be planned depending on the activity matrix and the corresponding filling of the Waste Bags. If the two Waste Bags are used one after another, seal off the full Waste Bag and open the clamp on the empty one.

When the activity matrix is created and all editing is completed, tap <ok> to proceed to the final setup check. To confirm, tap <yes>.

8.2.5 Final setup check



Screen 8.17: Final check

Check the height of the bag hangers and the vial holders as well as the parameter list (see Screen 8.17).

Parameters can only be revised but not edited at this point. To return to the previous screen, tap <undo>.

After confirming the parameter list, make sure to mix the labeled cells in the Reapplication Bag again before transfer to the chamber.

At this point, all preparative steps are complete, and the automated cultivation process can begin.

Tap <ok> to proceed. Tap <yes> to confirm the setup. The automated culture setup is initialized (see Screen 8.18).

8.2.6 Automated culture setup

The culture setup is performed automatically and includes the following steps:

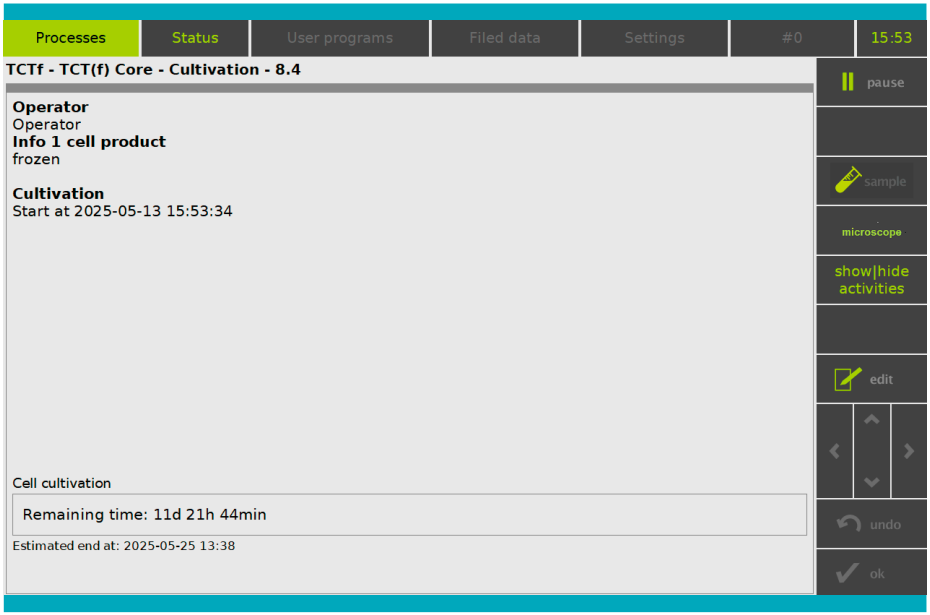
1. Priming of the chamber and the tubing set with medium.
2. Transfer of the selected amount of cells to the chamber.
3. Washing of the cells with medium.
4. Fill-up to 40 mL in the cultivation chamber.
5. Setup of aeration and temperature.

Mix the Reapplication Bag thoroughly before the automatic culture setup is initiated to ensure the correct cell seeding density.

If case 4 "Resume T cell cultivation" has been selected in chapter 3.2 ´Process´, only step 5 is executed.

IMPORTANT
All steps programmed in the activity matrix are performed after the culture setup. The culture setup is performed automatically in one step and is not part of the activity matrix. The culture setup cannot be modified.

8.3 Cultivation



Screen 8.18: Cultivation (Processes)

To change the activity matrix during cultivation, tap **<edit>**.

To show the current activity matrix, tap **<show/hide activities>**.

To make a photographic record of cells, tap **<microscope>**.

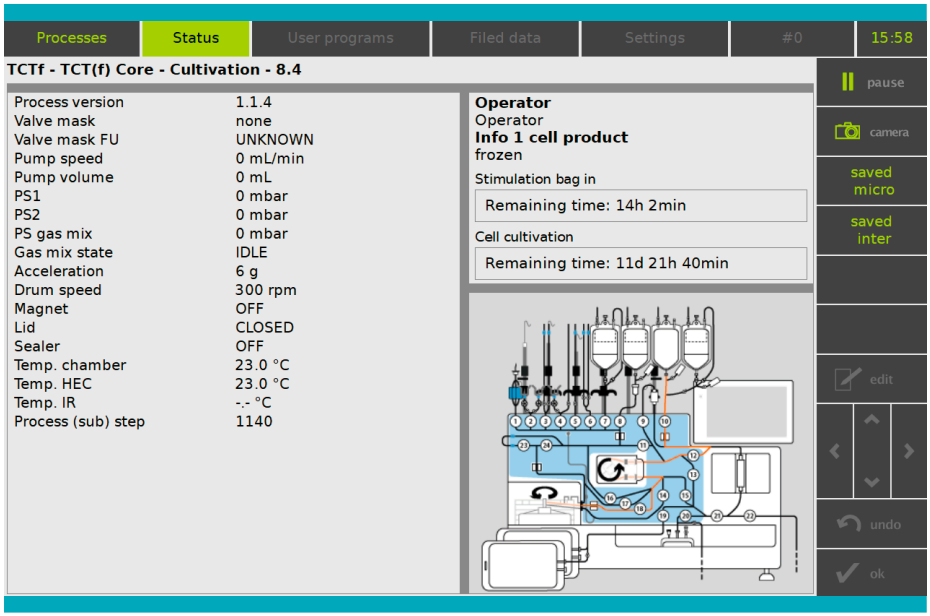
To take a sample during cultivation, tap **<sample>**. Alternatively, the activity "Sampling" can be programmed into the activity matrix.

For details refer to the following sections.

When programming the cultivation matrix, be aware: If one activity is not finished yet and the next one is supposed to start, the first activity will be completed. The following activity will be delayed. No activity will be skipped.

The activity "End of culture" is excluded from this rule and will always be executed as soon as it is due. If another activity is overdue as well, this activity will be skipped.

Always make sure that the time and date of the instrument is set correctly before starting the process.



Screen 8.19: Cell cultivation (Status)

After initial setup of the cultivation, the monitor shows the current step and the remaining time of the cultivation process in the <Status> screen.

The remaining enriched target cells can now be retrieved (e.g., to be frozen) by sealing off the Reapplication Bag. Do not seal off the Filtration Bag 2.

8.3.1 Monitoring of cultivation via sensor values

During the cultivation, several sensor values can be monitored on the <Status> screen. The pressure sensor "PS gas mix" is inside the gas mix unit and should show values between 0 mbar and 800 mbar during the setup and between 200 mbar and 800 mbar during cultivation.

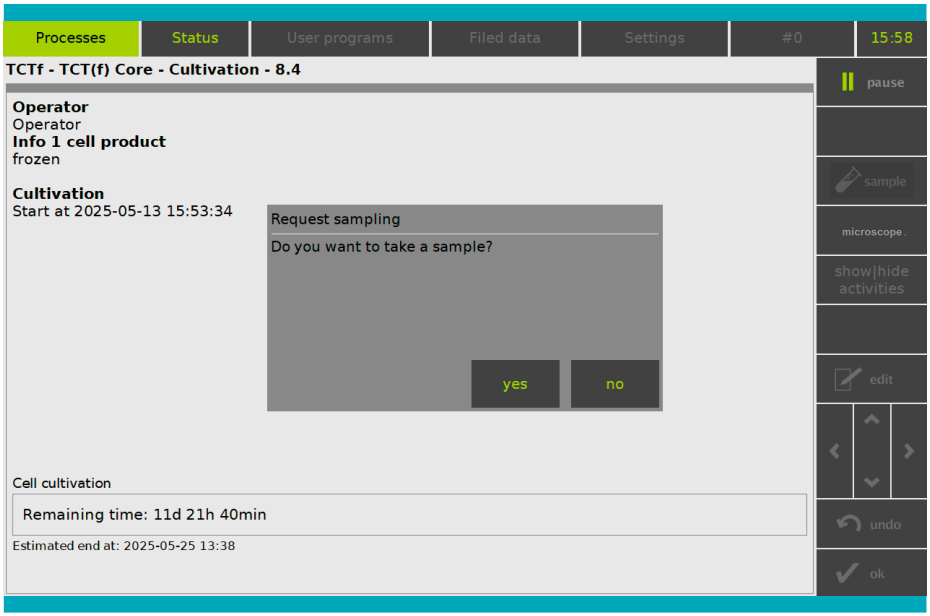
8.3.2 Sampling during cultivation

The process offers two sampling options during the culture phase.

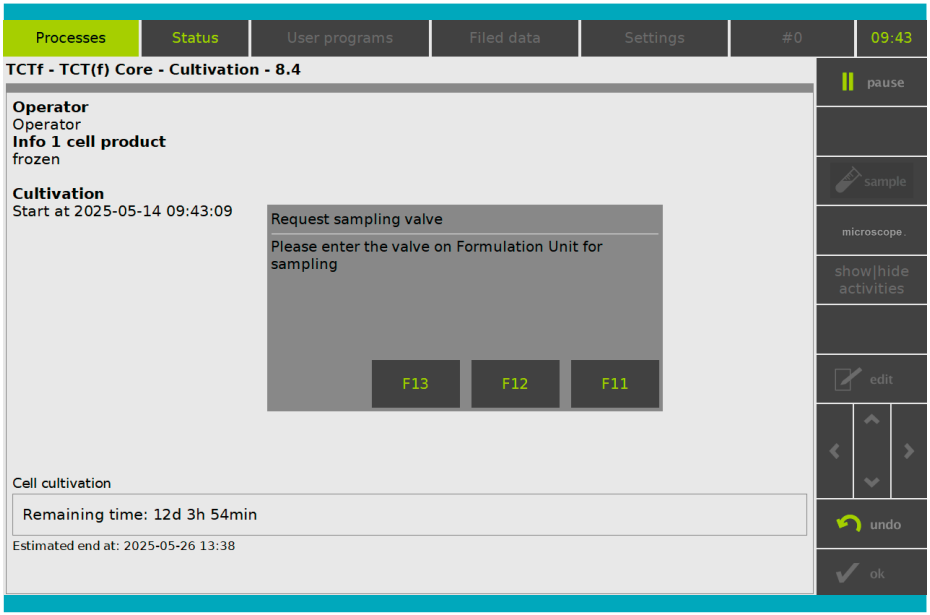
Option 1

Tap the <sample> button on the process screen at any time, when no activity or gas injection is currently performed.

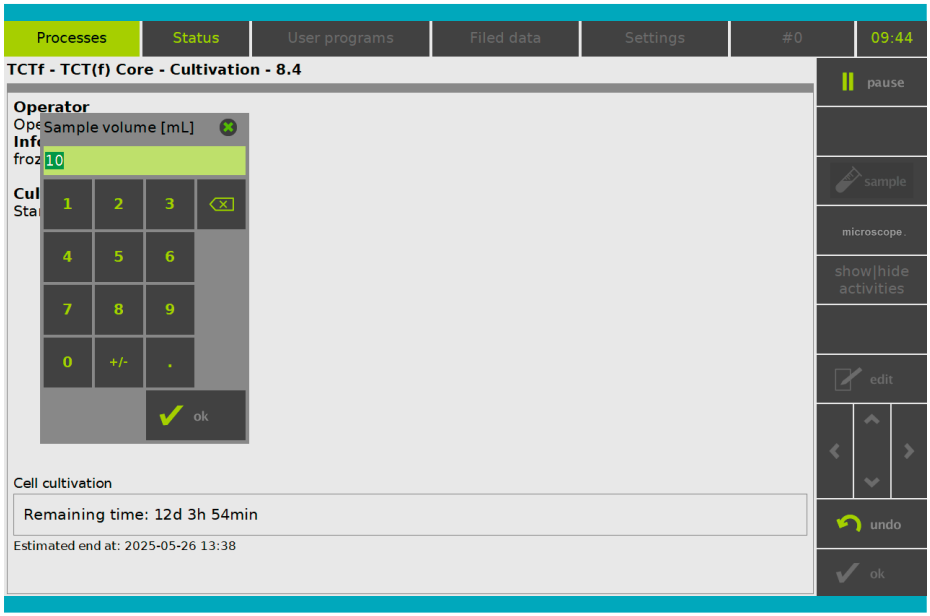
Tap <yes> to continue with the sampling and choose the target valve at the Formulation Unit and the sample volume.



Screen 8.20: Request sampling



Screen 8.21: Request sampling valve



Screen 8.22: Select sample volume

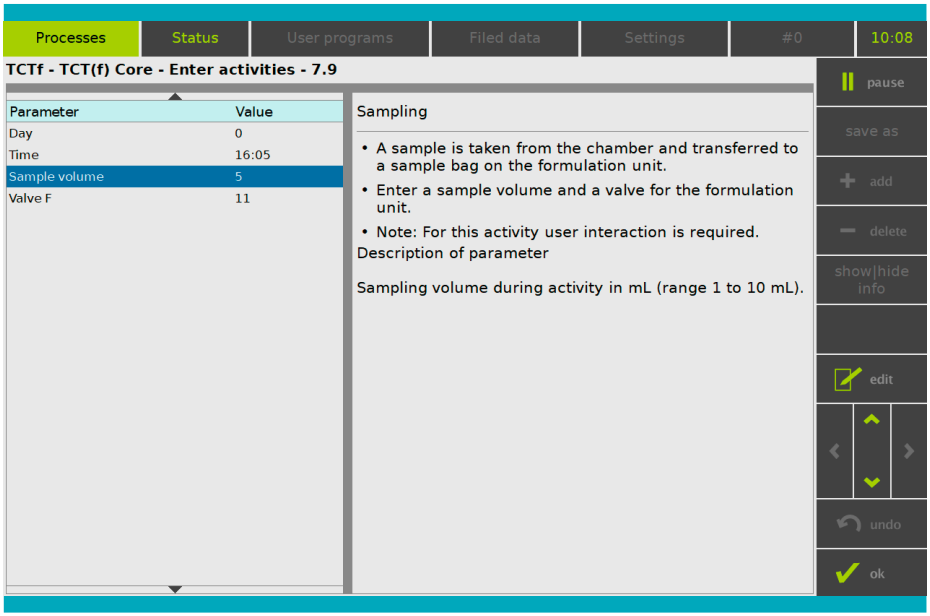


Screen 8.23: Prepare sampling

Option 2

Program the sampling activity into the activity matrix to perform sampling at a specified day and time.

Both options require user interaction.

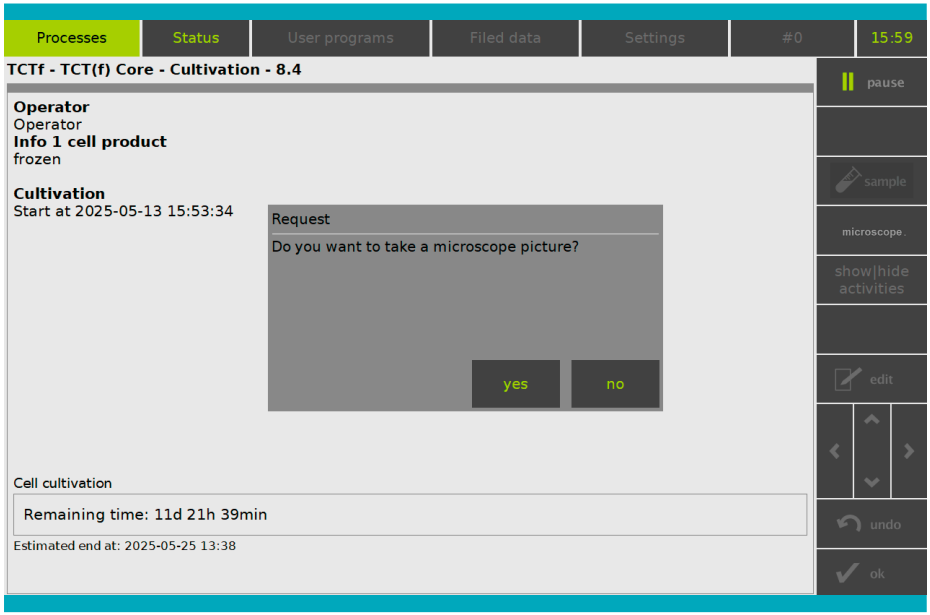


Screen 8.24: Sampling

For both sampling options confirm the sample collection and select one of the valves: F11, F12 or F13. Specify a sample volume between 1 mL and 10 mL. For sampling option 2 additionally, select the preferred day and time for sample collection.

Make sure that a QC bag is available at the chosen valve. In case there are two bags, make sure to clamp off one bag.

8.3.3 Taking microscope pictures during cultivation



Screen 8.25: Taking a microscope picture

To take a microscope picture during cultivation, follow the procedure described below:

- Tap <Processes>.
- Tap <microscope>.
- Tap <yes> to confirm taking a microscope picture.
- Tap <edit> to enter the desired position (1–20) and brightness (e.g., 100) for the picture.
  The camera will autofocus and take a picture.
- Tap <Status> and select the camera button to show the camera screen. The picture will be shown seconds later. To leave the camera view, tap <ok>.
- Tap <yes> to take another picture. Otherwise, tap <no> to return to the cultivation.

At higher cultivation volumes and during agitated culture (with an active shaker) the quality of the picture might decrease. This is mainly caused by light dispersion and by the fact that the cells are in suspension and not settled on the bottom of the chamber. Allow the cells to settle before taking a picture to increase picture quality.

8.3.4 Stimulation

IMPORTANT
Once the activity has started and a pop-up appears, it is not possible to change any parameters (e.g., time or volume). Make sure to have entered all parameters correctly. Once the pop-up is shown no gassing or temperature control is performed.

The activities "Stimulation bag" and "Stimulation vial" require user interaction.

For stimulation of the selected T cells, the activity "Stimulation bag" or "Stimulation vial" must be programmed into the activity matrix (see section ´Stimulation bag´).

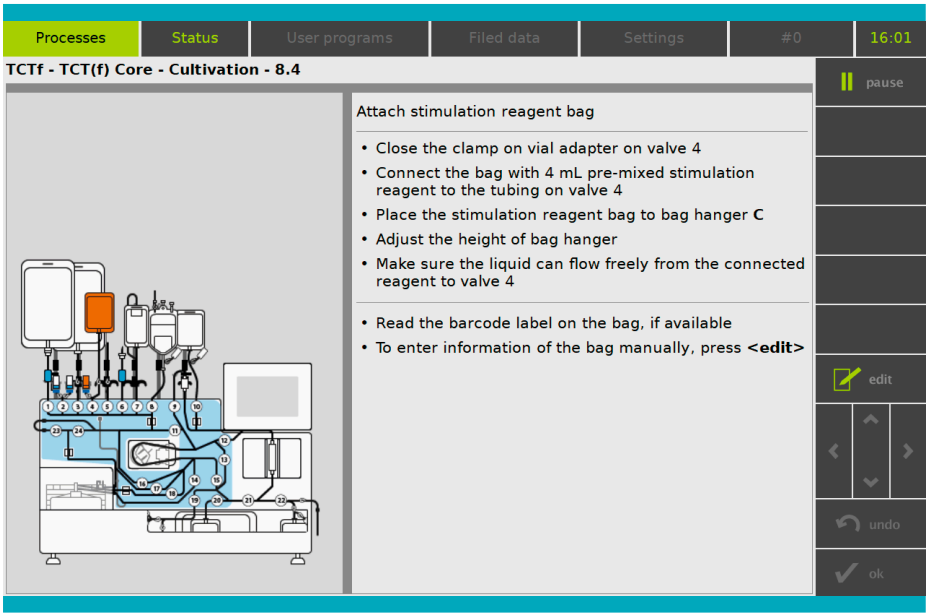
⚠ CAUTION

Risk of cell loss. Incomplete loading of the stimulation reagent can lead to delayed cell preparation.

- Make sure that the stimulation reagent has been loaded completely after the activity to ensure optimal activation results.

Stimulation bag

The stimulation bag should be prepared under sterile conditions in a bag that can be connected to the tubing set via sterile welding. Follow the specific instructions on the screen for the "Stimulation bag" activity (see Screen 8.26).



Screen 8.26: Connection of the stimulation reagent (bag)

IMPORTANT

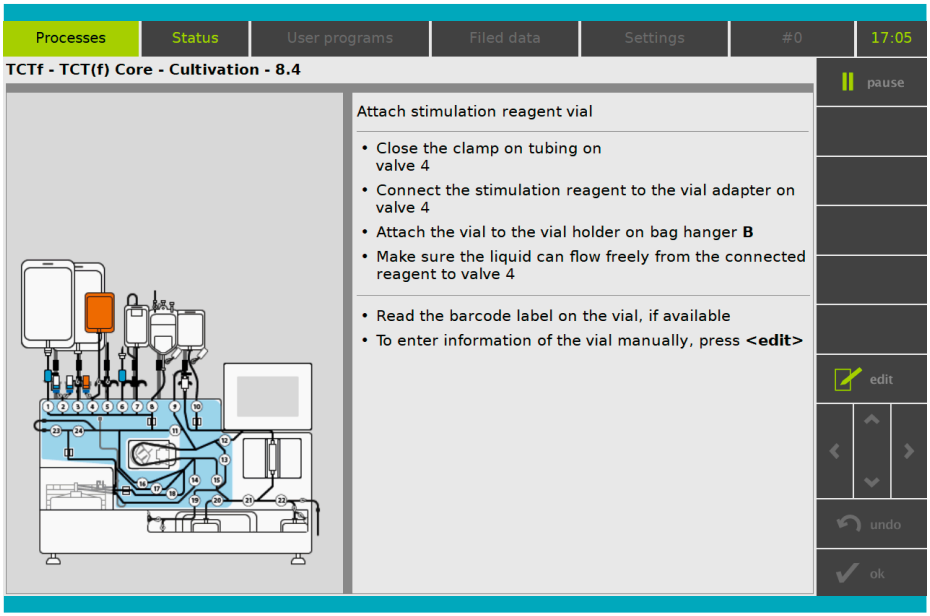
The volume (4 – 200 mL) must be programmed into the activity of the matrix during set up. Make sure the bag contains the exact volume which is programmed.

Stimulation vial

Follow the specific instructions on the screen for the "Stimulation vial" activity (see Screen 8.27).

IMPORTANT

It is mandatory to use MACS GMP T Cell TransAct as a stimulation vial. Connect the vial as described in the screen. Ensure that the MACS GMP T Cell TransAct is used in the correct dilution. The culture volume in the chamber must be 40 mL to achieve the correct dilution.



Screen 8.27: Connection of the stimulation reagent (vial)

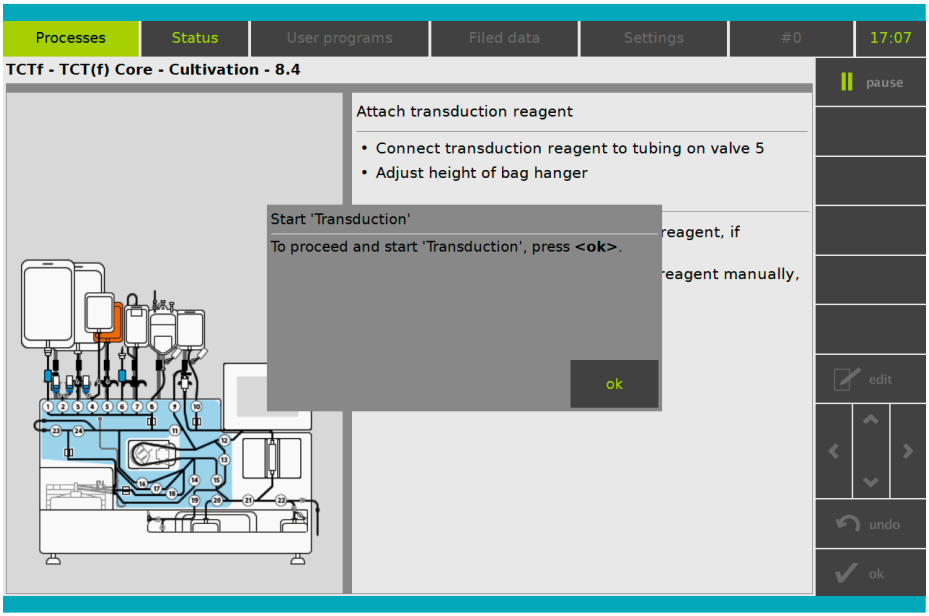
Read barcode label on the stimulation vial or tap <edit> to enter part number (P/N) and lot number (LOT) manually.

IMPORTANT
In case a vial is used for stimulation, ensure that the filter at the vial adapter on valve 4 is unused and dry. A used vial adapter must be replaced with a new "Single Vial Adapter".

After the activity the chamber volume will be 70 mL.

8.3.5 Transduction

IMPORTANT
Once the activity has started and a pop-up appears, it is not possible to change any parameters (e.g., time or volume). Make sure to have entered all parameters for the connection of the transduction reagent correctly. Once the pop-up is shown no gassing or temperature control is performed until confirmation.



Screen 8.28: Transduction

For transduction of the activated T cells, the activity "Transduction" has already been programmed into the activity matrix (see section 8.2.4 ´Setup of activity matrix´).

It is recommended to perform the transduction approx. 20 h after stimulation.

The activity "Transduction" will not start without confirmation by the user (see Screen 8.28).

When the scheduled time point is reached, user interaction is required. Follow the instructions on the screen to connect the viral vector bag.

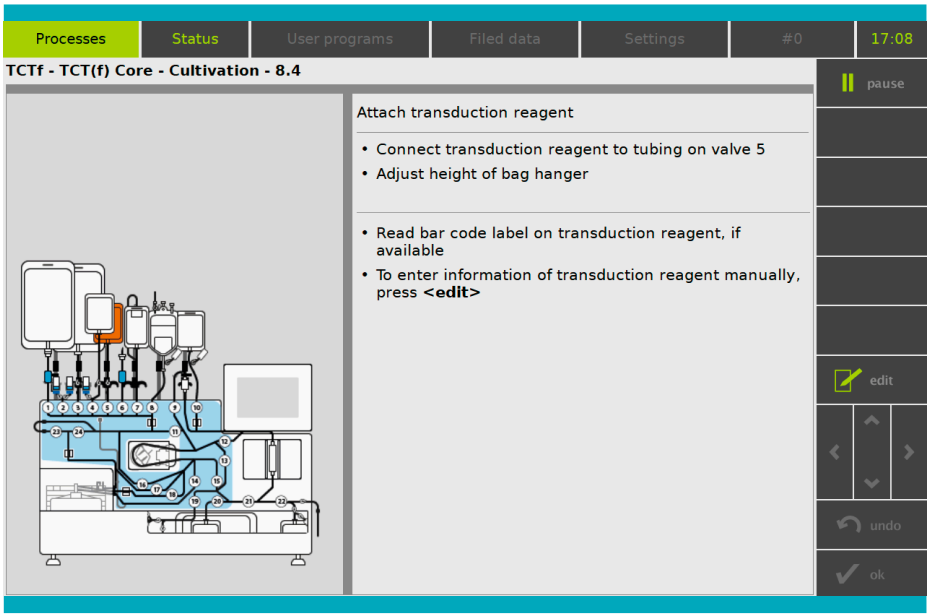
The viral vector should be prepared under sterile conditions in a bag that can be connected to the tubing set via sterile welding.

The viral vector must be in a volume between 5 mL and 100 mL.

It is recommended to use concentrated viral vector in a volume of 10 mL.
Only connect the exact volume that shall be used for transduction. The CliniMACS Prodigy will stringently pump the volume that is programmed into the activity matrix.

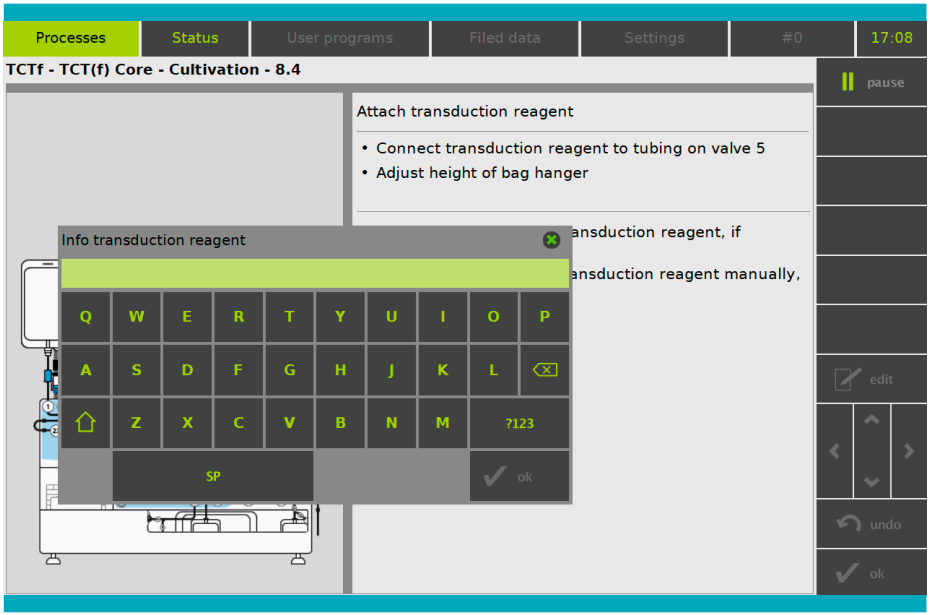
If the vector is in a much larger volume, consider reducing the volume of the culture prior to transduction using the activity "Volume reduction".

By adding the viral vector and the following rinsing steps, the volume of the culture in the chamber increases by the volume of the vector plus 20 mL medium used for rinsing.



Screen 8.29: Connection of viral vector

Use a sterile tubing welder to connect the viral vector to the tubing on valve 5.



Screen 8.30: Entering information on viral vector

Tap <edit> and enter information on the viral vector with the keyboard shown on the screen.

8.3.6 Culture wash

The activity "Culture wash" will be executed automatically.

It is recommended to perform a culture wash on day 3 to remove excess activation reagent and viral vector particles.

⚠ CAUTION

Risk of allergic reaction or contamination of cell product. In case of insufficient washing of the cell product after stimulation and transduction, the final cell product could include leftover viral vector or stimulation reagents. The user is responsible for testing.

- Use the default activity matrix for sufficient washing.

IMPORTANT

The amount of medium needed for the culture wash depends on the cycles programmed into the activity. For 1, 2, and 3 cycles a respective volume of 600 mL, 860 mL, and 1 120 mL must be available in the bag on valve 3.

After the culture wash activity, the total culture volume is always 200 mL.

Use the activity "Medium bag exchange" to attach a new medium bag, if necessary.

8.3.7 Volume reduction and spin

The activities "Volume reduction" and "Spin" will be executed automatically.

The activity "Volume reduction" will reduce culture volume to the desired volume by centrifugation and supernatant removal.

Make sure that there is medium connected to valve 3. The minimal target volume is 10 mL.

Spinoculation might be used to enhance transduction efficiency by spinning the cells and virus at 400 ×g for up to 8 h. During spinoculation the temperature can be adjusted between +18 to +39 °C (+64 to +102 °F).

IMPORTANT

In the "Spin activity" the temperature can be adjusted. For this purpose, it is highly recommended to receive a temperature adjustment and validation procedure for the instrument. If the instrument has no temperature offset values, a warning will appear stating that no temperature offset values could be detected on the instrument (see section 8.2.3 ´Input of CO_2 and temperature parameters´).
In this case the adjusted temperature cannot be guaranteed. For further information contact Miltenyi Biotec Technical Support.

8.3.8 Medium and Waste Bag exchange

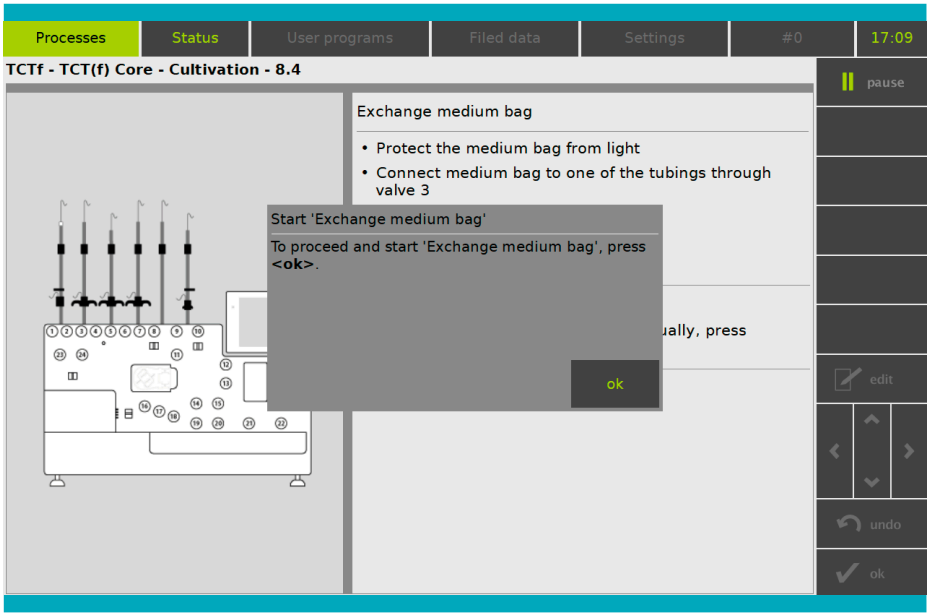
⚠ CAUTION

Risk of cell loss. Medium can be insufficient for the whole culture period.

- Make sure to attach enough medium.
- Before starting the process, calculate the required amount of medium

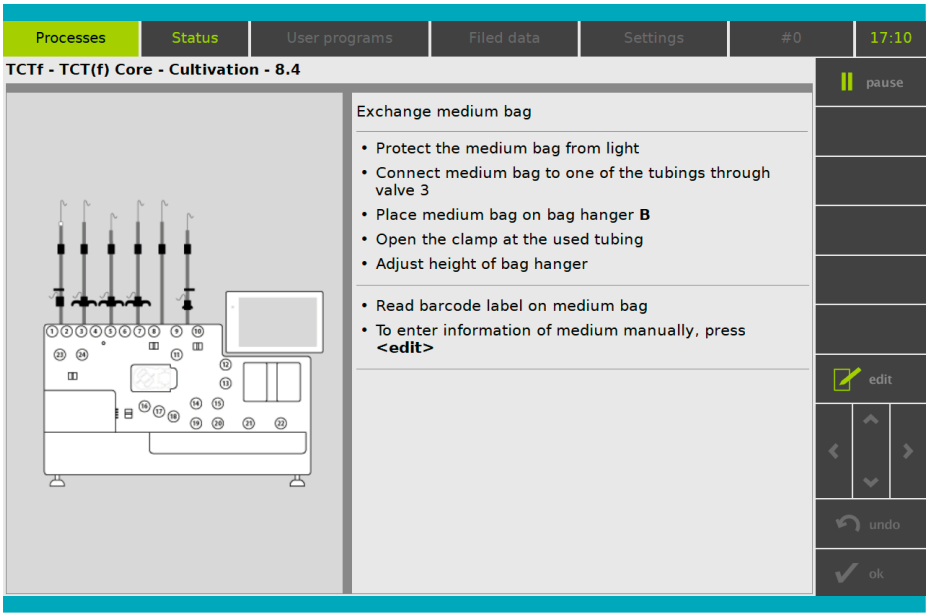
IMPORTANT

Once the pop-up is shown no gassing or temperature control is performed until confirmation.



Screen 8.31: Start of activity Medium bag exchange

Refer to chapter 6 ´Preparative steps´of this user manual for the preparation of the medium.



Screen 8.32: Connection of medium bag

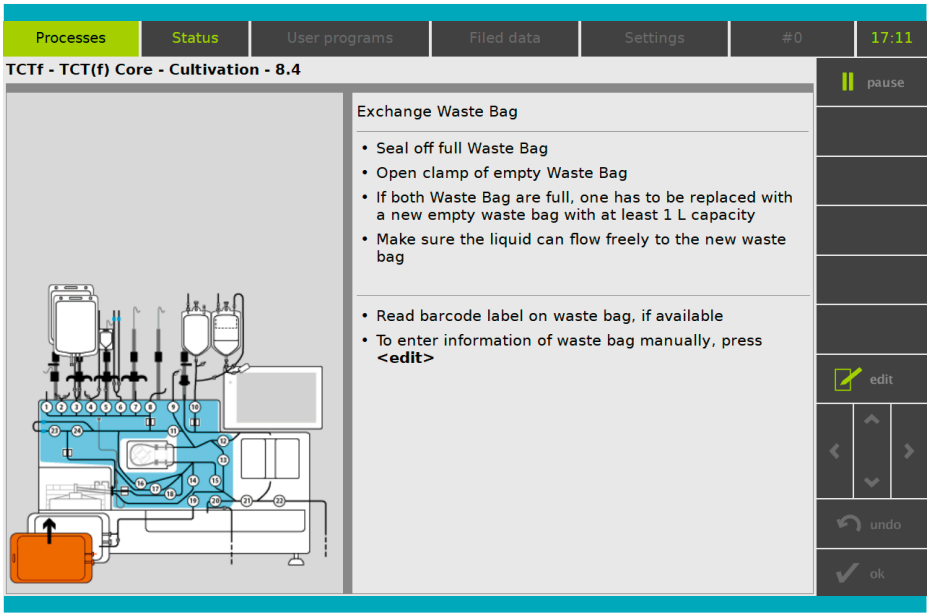
When the programmed time point for the activity "Medium bag exchange" is reached, user interaction is required. Follow the instructions on the screen to connect a new medium bag (for details see section 8.4 ´End of culture´).

Read the barcode label on the medium bag. To manually enter the information, tap <edit>, then tap <ok>.

To enter information regarding supplements, tap <edit>. Confirm the entered values with <ok> to complete the activity and return to cultivation.

In case three medium bags shall be connected, make sure to use a 3-way Tube Adapter and ensure each bag is connected to valve 3.

IMPORTANT
It is strongly recommended that the user monitors the medium bag capacity to prevent any errors in the process.



Screen 8.33: Connection of new empty waste bag

When the programmed time point for the activity "Waste Bag exchange" is reached, user interaction is required. Follow the instructions on the screen to connect a new empty Waste Bag (see Screen 8.33).

Read the barcode label on the Waste Bag. To enter the information manually, tap <edit> , then tap <ok>. Confirm the entered values with <ok> to complete the activity and return to cultivation.

Ensure that the waste liquid can flow freely to the available Waste Bag in use.

⚠ WARNING

Risk of biological hazard. The Waste Bag may comprise infectious biological material or residual viral vector.

- Standard procedures for handling biological materials have to be followed.
- Dispose of the used Waste Bag as biohazardous material according to the standard operating procedures of the institution.
- Consider the genetic engineering biosafety level of the used viral vector for waste disposal.

8.3.9 Feed and Media exchange

The activity "Feed" and "Media exchange" will be executed automatically.

When the programmed time for activity "Feed" and "Media exchange" is reached (see section 8.2.4 ´Setup of activity matrix´), the activity will start automatically (no user interaction required).

Make sure that there is sufficient medium in the medium bag connected to the selected valve (default is valve 3).

If a different valve than valve 3 is selected, ensure that there is always medium connected to valve 3 for tubing set rinsing which is automatically performed every 10 hours.

Use the activity "Medium bag exchange" to attach a new medium bag, if necessary.

8.3.10 Temperature change

IMPORTANT
It is highly recommended to receive a temperature adjustment and validation procedure for the instrument. If the instrument has no temperature offset values, a warning will appear stating that no temperature offset values could be detected on the instrument (see Screen 8.7 on page 88). In this case the adjusted temperature cannot be guaranteed. For further information contact Miltenyi Biotec Technical Support.

The activity "Temperature change" (see section 8.2.4 ´Setup of activity matrix´) will be executed automatically and will continuously run in the background.

During cultivation the temperature can be adjusted by using this activity. If a temperature adjustment was performed, the desired temperature can be entered and the temperature for the chamber will be set to the defined value.

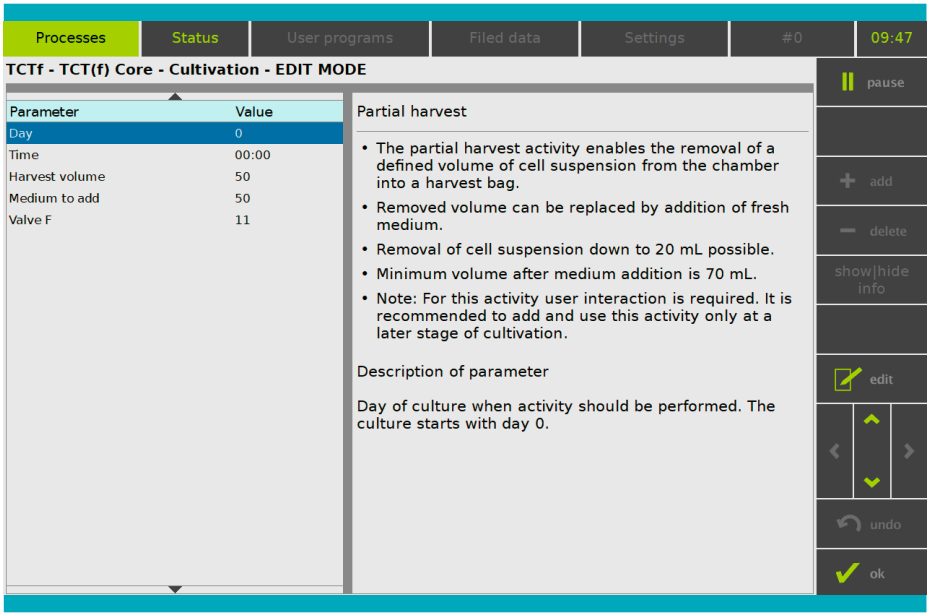
8.3.11 Partial harvest

⚠ CAUTION

Risk of inadequate quantity of cells or impaired potency of cells. Using the activity "Partial harvest" for cell adjustment can lead to incorrect cell concentration.

- It is not recommended to use the activity "Partial harvest" for adjustment of specific cell concentrations

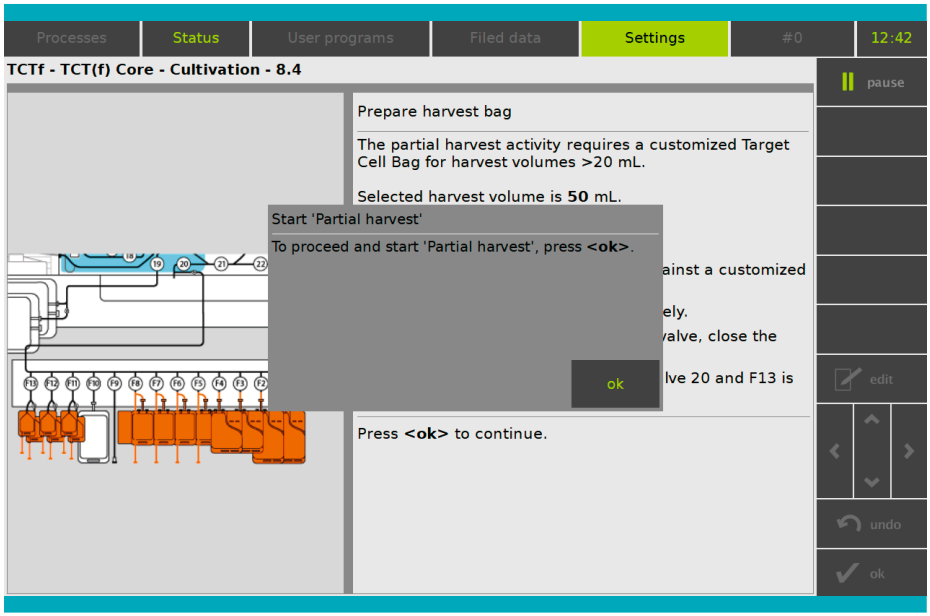
The partial harvest activity can be programmed into the activity matrix and requires user interaction.



Screen 8.34: Partial harvest

Choose day and time, the harvest volume, and the medium volume that will be added afterwards. Select one of the valves: F11, F12, F13.

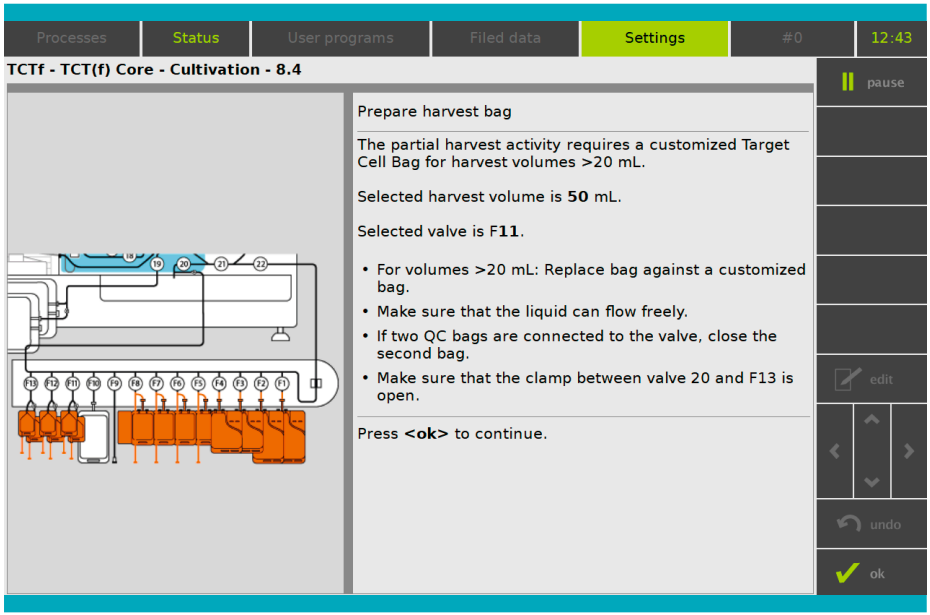
The minimum harvest volume is 10 mL. Always leave at least 20 mL in the chamber. After harvest volume removal, medium can be added up to a final volume of 250 mL in the chamber.
The final culture volume after the partial harvest needs to be at least 70 mL.



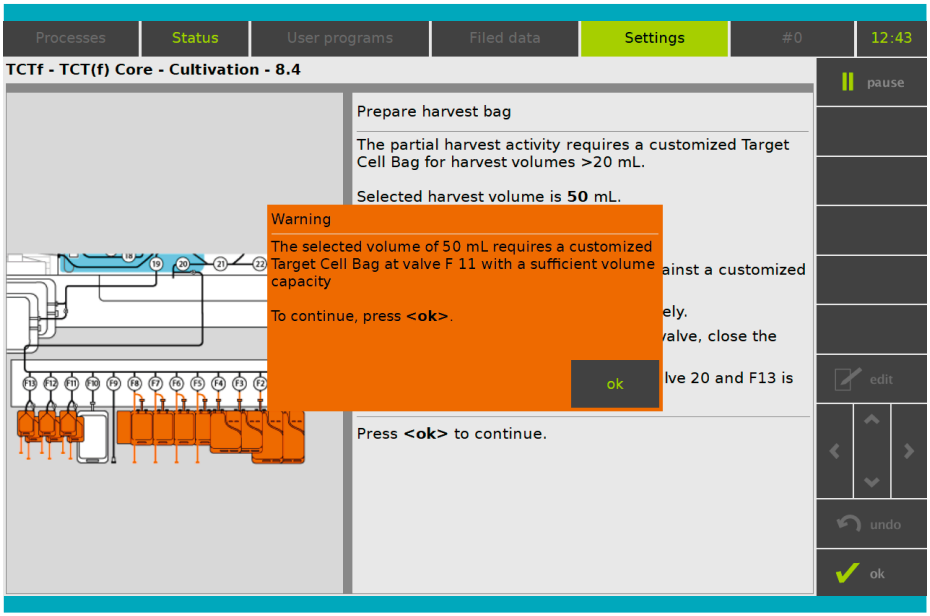
Screen 8.35: Start partial harvest

IMPORTANT

Once the pop-up is shown no gassing or temperature control is performed until confirmation.



Screen 8.36: Prepare harvest bag



Screen 8.37: Customized Target Cell Bag required

For a harvest volume higher than 20 mL connect a customized bag by sterile welding. In case there are two bags connected to the target valve, make sure to clamp off the unused bag.

8.4 End of culture

Choose between five end of culture types (see Screen 8.38). The end of culture type must be programmed into the activity matrix during set up (see section 8.2.4 ‘Setup of activity matrix’).

⚠ CAUTION

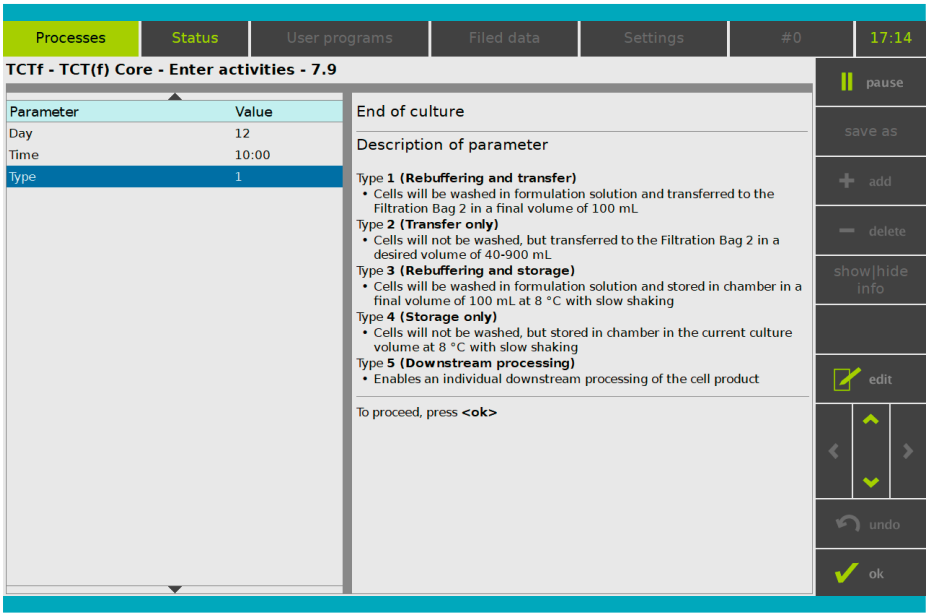
Risk of low performance. Cultivation times longer than 12 days can cause lower cell viability and might cause a loss of the cell product.

- It is recommended to perform the end of culture activity on day 12.

⚠ CAUTION

Risk of loss of cell product or low performance. If end of culture (type 1, 3 or 5) is performed with a formulation solution other than the CliniMACS Formulation Solution, process errors or reduced cell quality can occur.

- It is recommended to use the CliniMACS Formulation Solution.
- If using any other formulation solution, make sure, the solution is suitable for the process.



Screen 8.38: End of culture – Choice between five different types

End of culture type 1: Rebuffering & transfer

Cells will be rebuffered in formulation solution and transferred into the Filtration Bag 2 in a final volume of 100 mL.

End of culture type 2: Transfer only

Cells will be directly transferred from the chamber to the Filtration Bag 2. Optionally, the bag can be filled up with medium to an intended volume of up to 900 mL.

End of culture type 3: Rebuffering and storage

Cells will be rebuffered in formulation solution and stored in the chamber in a final volume of 100 mL at 8 °C (46 °F) with slow shaking.

End of culture type 4: Storage only

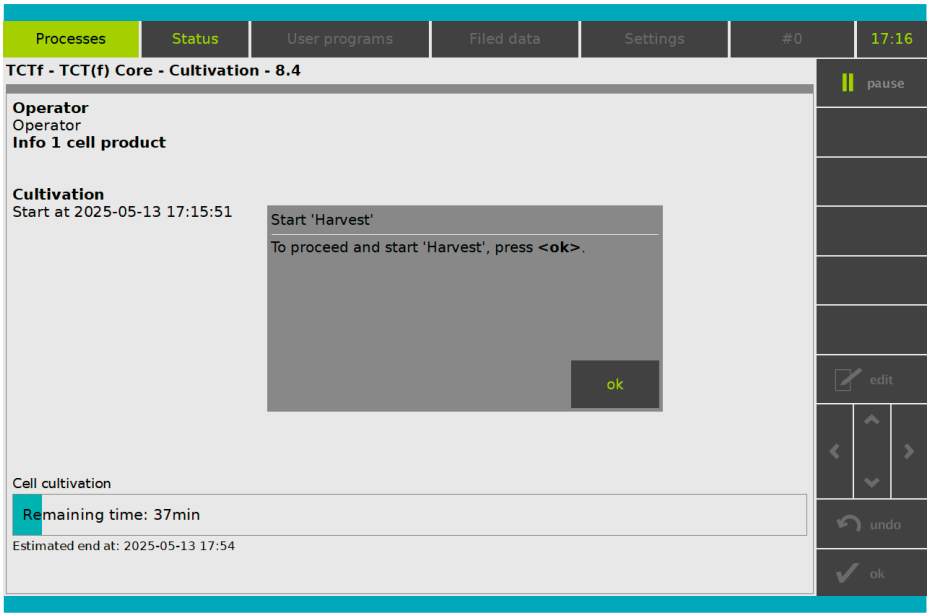
Cells will be stored in the chamber in the current culture volume at 8 °C (46 °F) with slow shaking.

End of culture type 5: Downstream processing

Cells will be washed in formulation solution, filtrated and formulated in a desired concentration, either for direct infusion (fresh) or for cryopreservation (frozen), followed by the automated filling of the drug product.

IMPORTANT

To start formulation and filling, use End of culture type 5 which includes these activities. End of culture type 5 is included in the default matrix.



Screen 8.39: End of culture – Start Harvest

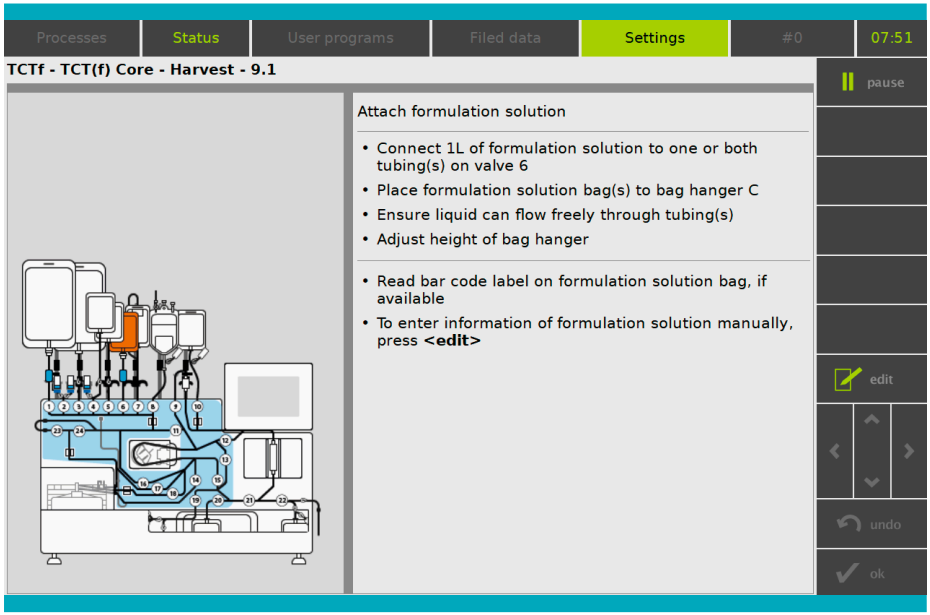
The harvest will not start without confirmation by the user (see Screen 8.39). Immediately start the harvest when asked in the pop-up.

When the programmed time for "End of culture" is reached (see section 8.2.4 ´Setup of activity matrix´) user interaction is required.

IMPORTANT

It is not possible to change any parameters of the end of culture activity at this point. Proceed immediately when the pop-up appears as temperature monitoring and gassing is not maintained at this point.

8.4.1 End of culture type 1

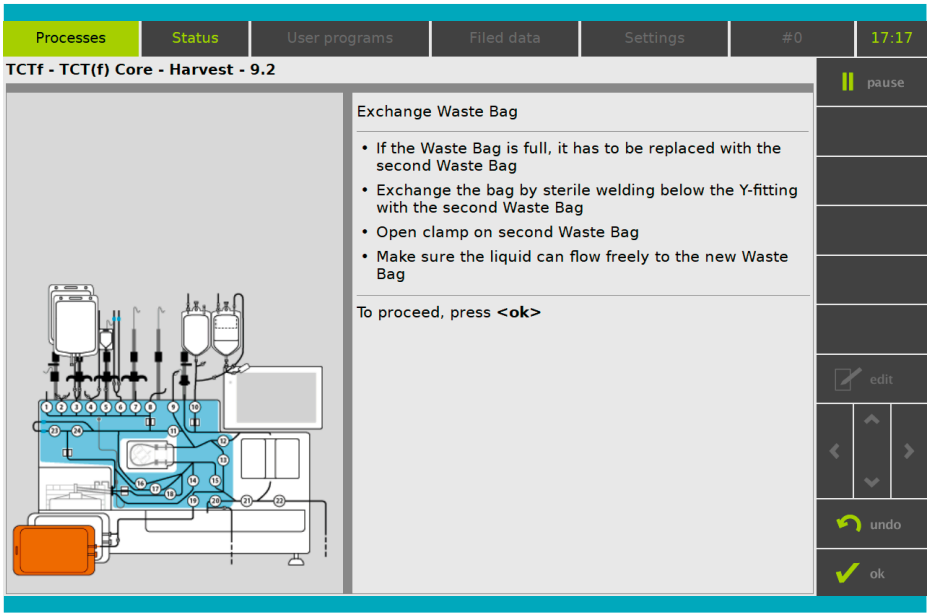


Screen 8.40: Attachment of formulation solution

Connect the formulation solution via sterile welding to the tubing above valve 6 (e.g., for CliniMACS Formulation Solution) and clamp the other unused line.

Read the barcode label on the formulation solution bag or tap <edit> to enter the information manually (see Screen 8.40).

To continue, tap <ok>.



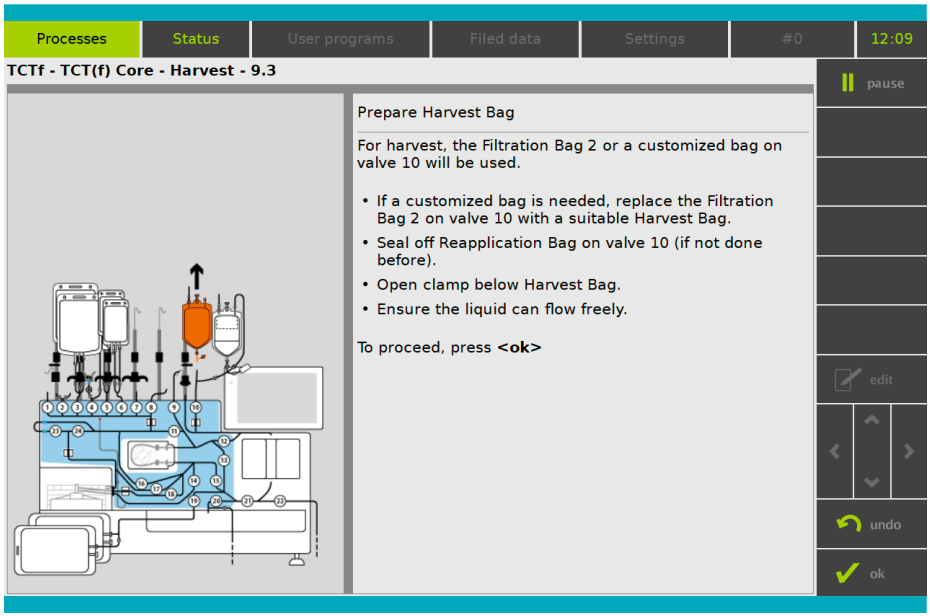
Screen 8.41: Exchange of waste bag

Waste Bag exchange is only necessary if the capacity of the current bag is nearly reached, and additional waste liquid capacity is required.

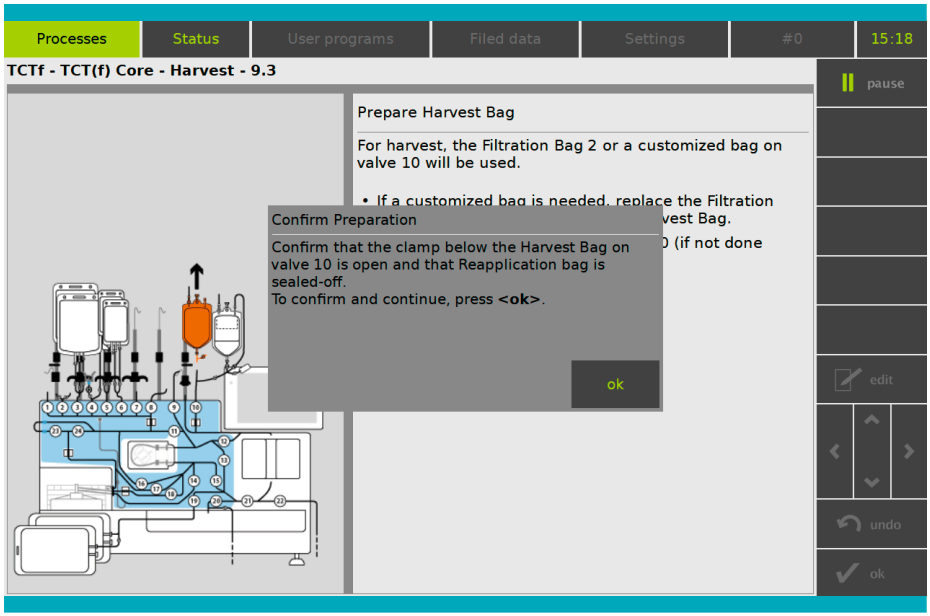
If required, connect a new empty Waste Bag via sterile welding (see Screen 8.41).

To continue, tap <ok> . If an exchange of the Waste Bag is not required, tap <ok> directly.

During the automated rebuffering and harvesting step the cells in the chamber are washed twice with the formulation solution and are then transferred to the harvest bag/Filtration Bag 2 on valve 10.



Screen 8.42: Prepare bag for harvest



Screen 8.43: Confirm preparation

Cell filtration is an option when harvesting target cells. For harvest, the Filtration Bag 2 or a customized bag on valve 10 is used.

If filtration of the cells is not required, the Filtration Bag 2 can be replaced with a suitable harvest bag.

IMPORTANT

If replacing the Filtration Bag 2, connect a suitable harvest bag by sterile welding in the lower part of the tubing before the branch to the QC pouch (see Figure 8.1).

Ensure that the clamp below the harvest bag is open and that the liquid can flow freely.

Follow the on-screen instructions to prepare the harvest bag. The final volume of the harvested cell product will be 100 mL.

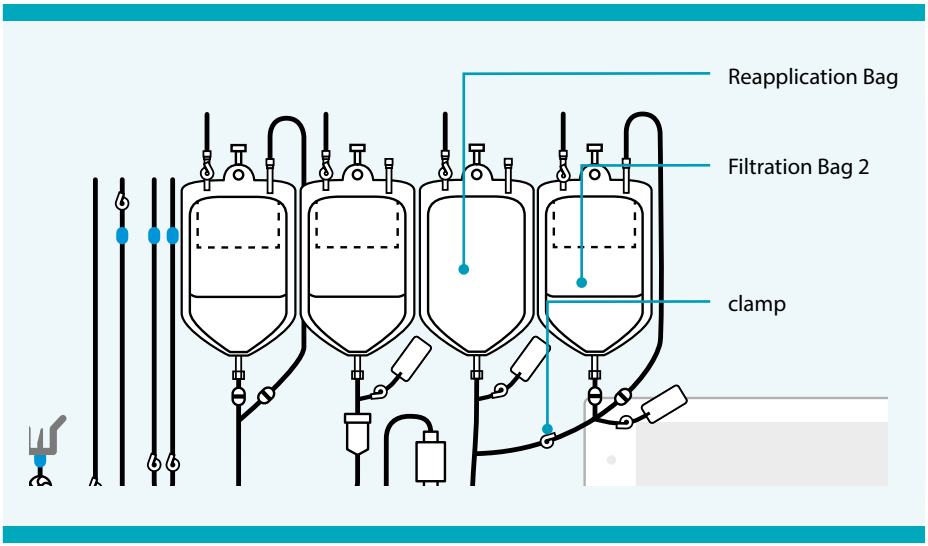


Figure 8.1: Reapplication Bag and clamp to Filtration Bag 2

⚠ CAUTION

Risk of cell loss. If the Reapplication Bag is not sealed off and/or the clamp to the Filtration Bag 2 is closed, the cells are transferred partly or completely into the Reapplication Bag and not in the Filtration Bag 2.

- Ensure the Reapplication Bag is detached and the path to the Filtration Bag 2 is open.

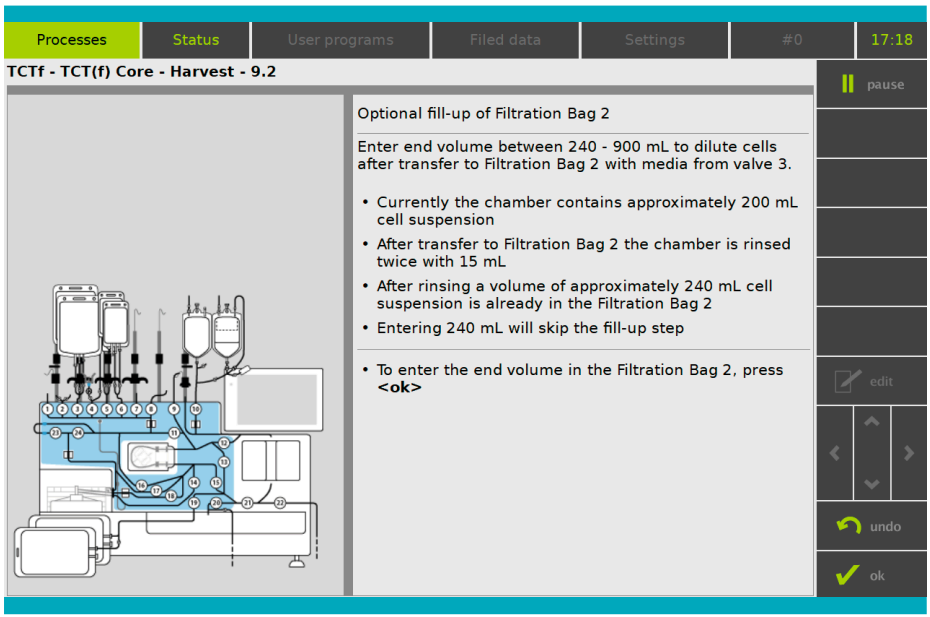
8.4.2 End of culture type 2

If required, exchange the Waste Bag. Connect a new empty Waste Bag via sterile welding (see Screen 8.41).

The activity end of culture type 2 transfers the cell suspension to the Filtration Bag 2. After the transfer, the chamber is rinsed twice with 15 mL of medium. The tubing set is rinsed once with 10 mL of medium. At the end of the activity the volume in the Filtration Bag 2 will be the current culture volume before transfer plus 40 mL.

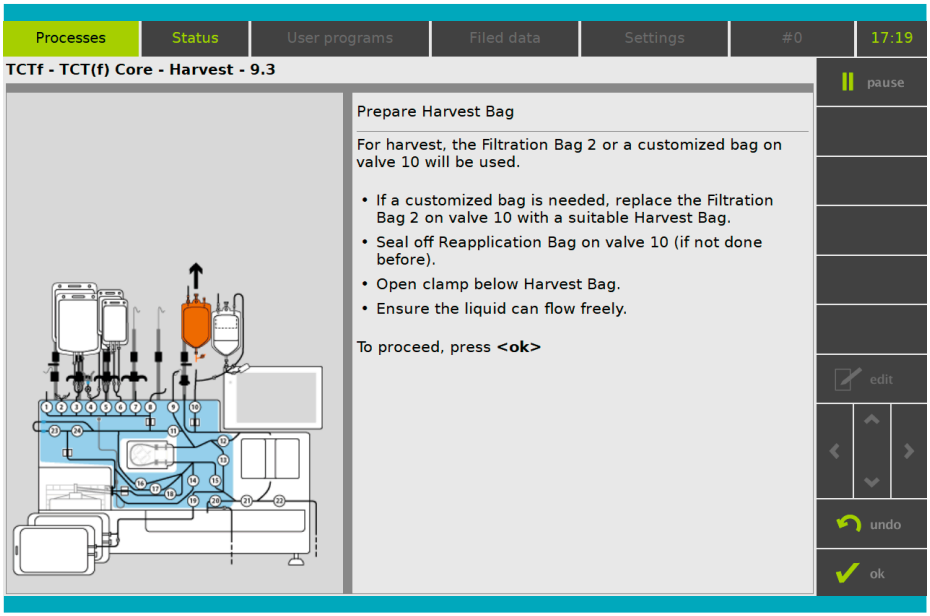
Optionally, the cell suspension in the Filtration Bag 2 can be automatically filled with medium to an intended volume of up to 900 mL.

IMPORTANT
The Filtration Bag 2 has a maximal capacity of 500 mL. It is recommended to fill the bag with maximal 300 mL of cell suspension to enable sufficient mixing and safe handling of the bag after harvest. Take this into account when programming the optional fill-up. Do not exceed the recommended filling volume of 300 mL when using Filtration Bag 2.



Screen 8.44: Optional medium fill-up during end of culture type 2

By setting the end volume to the current culture volume plus 40 mL (rinse volume), no additional fill-up will be performed (see Screen 8.44).
For volumes larger than 300 mL, the Filtration Bag 2 must be replaced with a customized bag with sufficient volume capacity by sterile welding (see section 8.4.1 ´End of culture type 1´ and Screen 8.45).



Screen 8.45: Preparation of Target Cell Bag or customized bag during end of culture type 2

8.4.3 End of culture type 3

Attach the formulation solution (see section 8.4.1 ´End of culture type 1´).

If required, exchange the Waste Bag. Connect a new empty Waste Bag via sterile welding (see Screen 8.41).

Cells will be rebuffered in formulation solution and stored in the chamber in a final volume of 100 mL at 8 °C (46 °F) with slow shaking.

⚠ CAUTION

Risk of low performance. There is no time limit to stop the process when the cells are stored in the chamber. Keep the cells under storage conditions as long as preparations for downstream processes are performed.

- Proceed as soon as possible to ensure cell viability.

8.4.4 End of culture type 4

In end of culture type 4 cells are stored in the chamber in the current culture volume and medium at 8 °C (46 °F) with slow shaking.

⚠ CAUTION

Risk of low performance. There is no time limit to stop the process when the cells are stored in the chamber. Keep the cells under storage conditions as long as preparations for downstream processes are performed.

- Proceed as soon as possible to ensure cell viability.

8.4.5 End of culture type 5

⚠ CAUTION

Risk of cell loss. If the Reapplication Bag is not sealed off and/or the clamp to the Filtration Bag 2 is closed, the cells are transferred partly or completely into the Reapplication Bag and not in the Filtration Bag 2.

- Ensure the Reapplication Bag is detached and the path to the Filtration Bag 2 is open.

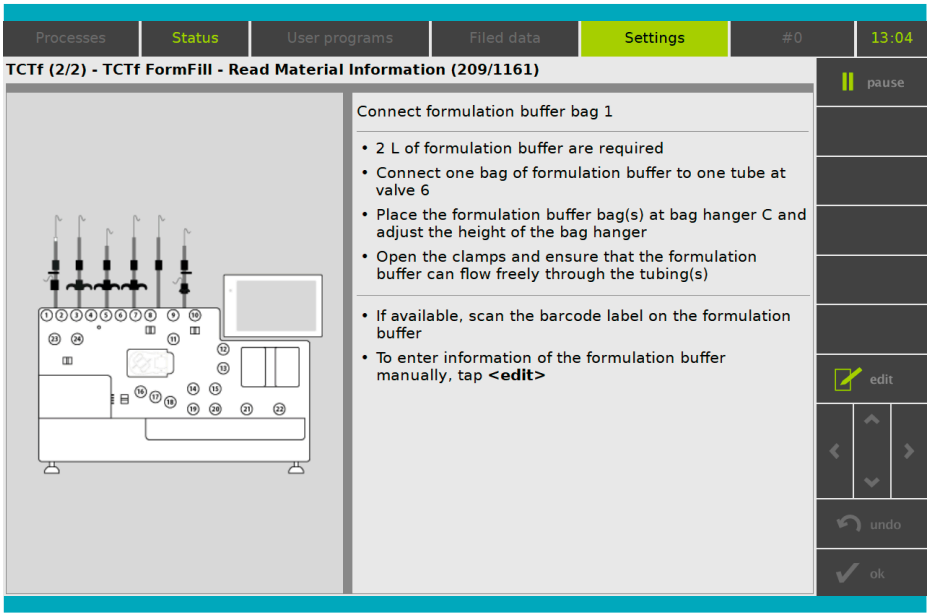
For details see Figure 8.1.

Preparation:

If required, exchange the Waste Bag. Connect a new empty Waste Bag via sterile welding (see Screen 8.41).

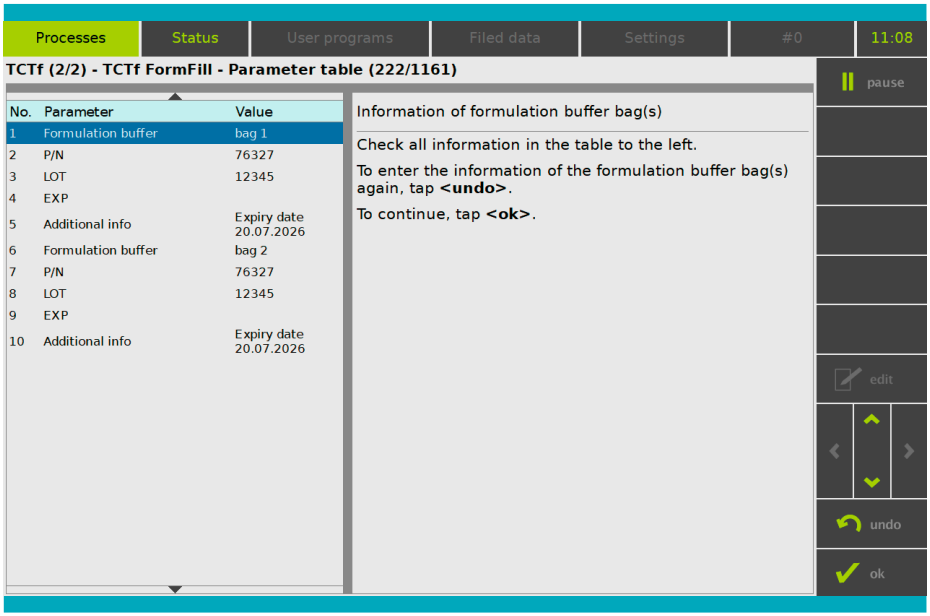
Connect two 1 L bags of formulation solution via sterile welding to the respective tubings above valve 6 (e.g., for CliniMACS Formulation Solution).

Read the barcode label on the formulation solution bags. To manually enter the information, tap **<edit>**, then tap **<ok>** (see Screen 8.46).



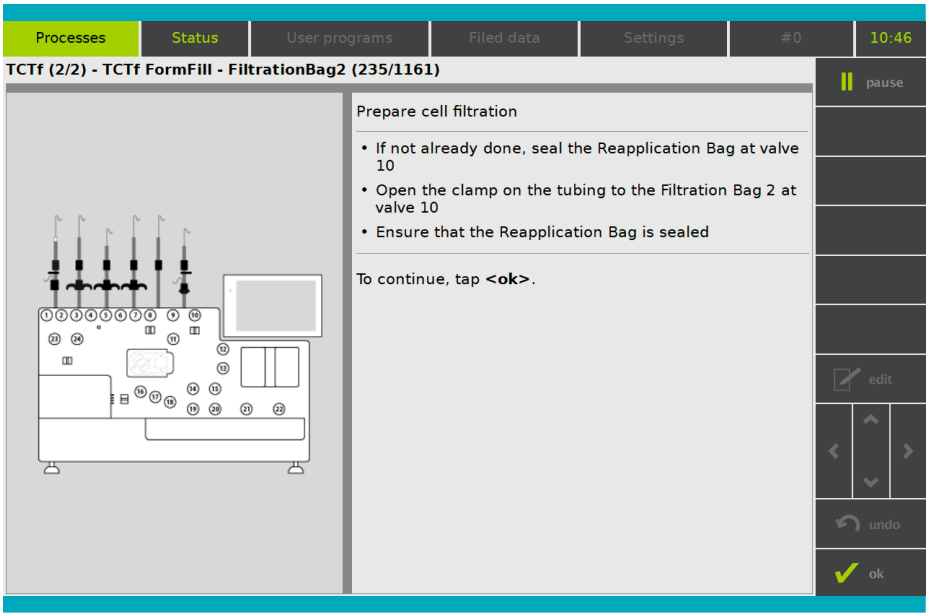
Screen 8.46: Connect formulation buffer

The information and input for the formulation solution is summarized on the screen (see Screen 8.47).



Screen 8.47: Parameter table for formulation solution

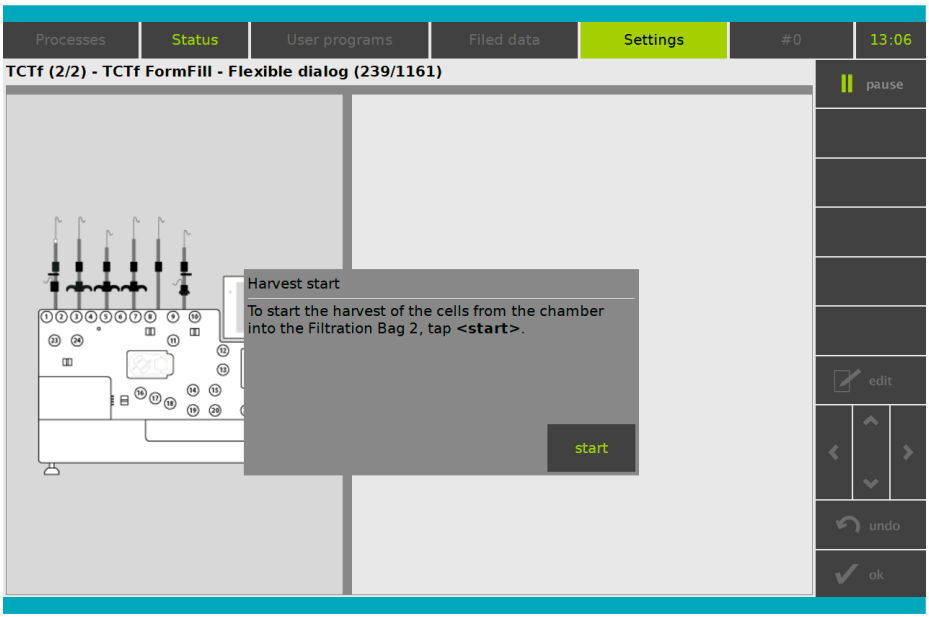
Follow the instructions on the screen.



Screen 8.48: Prepare cell filtration

To start the harvest to the Filtration Bag 2, tap <start>.

The cells will be washed and rebuffered in formulation solution, followed by transfer to the Filtration Bag 2 for filtration and chamber cleaning. Afterwards the cells will be transfered back into the chamber for sampling.

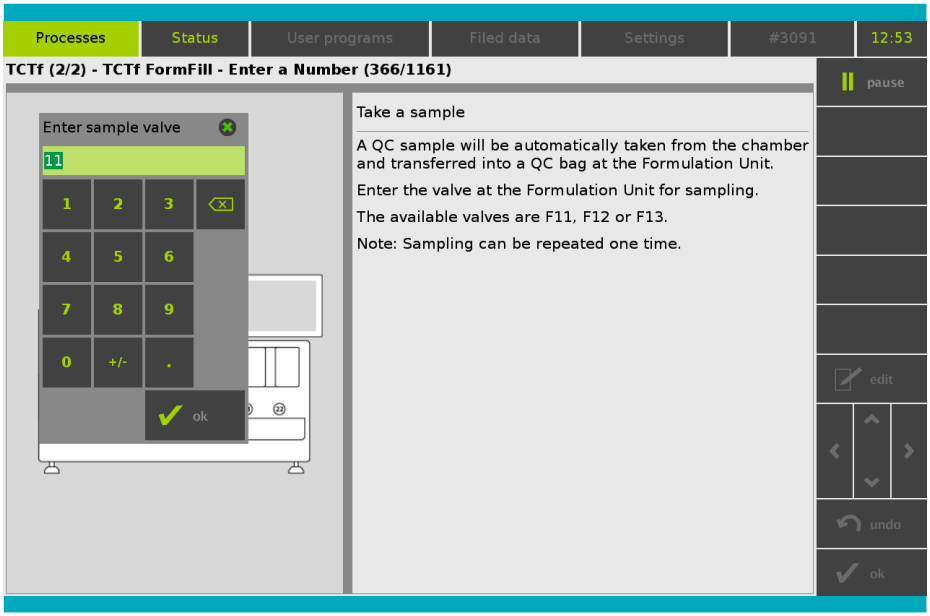


Screen 8.49: End of culture type 5 - Start of harvest

Sampling

Select one of the valves F11, F12 or F13 to take the sample from the rebuffered and filtrated cells. Taking a sample can be repeated once.

A QC Bag must be in place at the chosen valve, with an open pathway to the QC bag and an unclamped connection between valve 20 and F13.
Determine the current cell concentration of the target cell type (e.g., $CD3^+$ cells or CAR^+ cells) in the sample.



Screen 8.50: End of culture type 5 - Take a sample

Determine the current cell concentration of the target cell type (e.g., $CD3^+$ cells or CAR^+ cells) in the sample.

Product bag priming

⚠ WARNING

Risk to patients. Non-primed Product Bags could contain particles which pose a risk to patient safety.

- Only use primed Product Bags.

⚠ CAUTION

Risk of low performance. Due to the priming a minimal left-over volume of formulation solution remains in the Product Bags. Therefore, the final cell product might be slightly diluted, influencing small filling volumes more than high ones.

- Use overage if required.
- If using a Product Bag for QC sampling, it is recommended to prepare it the same way and fill it with a represantative volume.

⚠ CAUTION

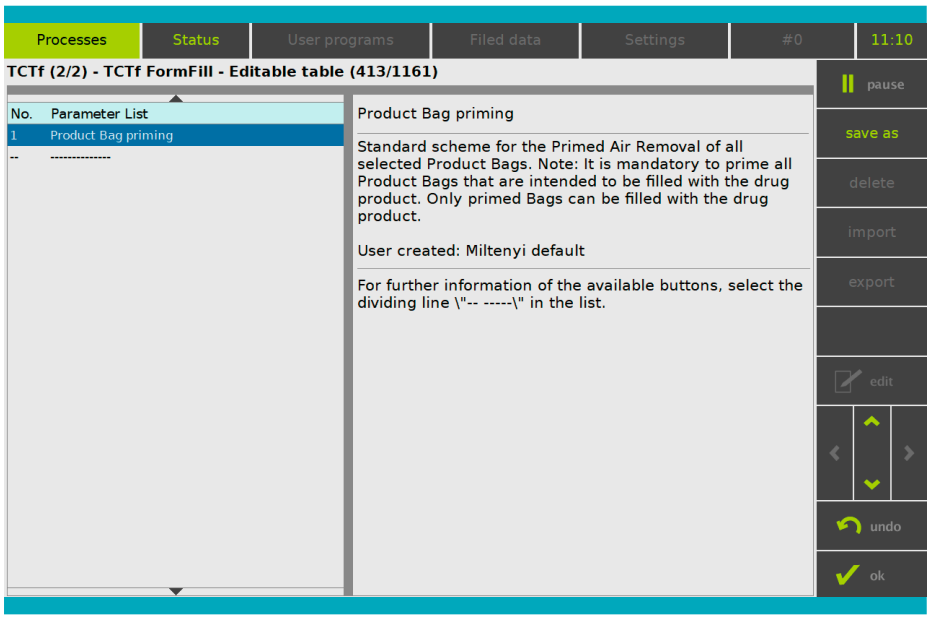
Risk of low performance. Air in the Product Bag might influence the quality of the drug product during transport (fresh formulation) or during freezing process (frozen formulation).

- Make sure to prime all required bags.
- It is important to remove all the air from the bag during priming.

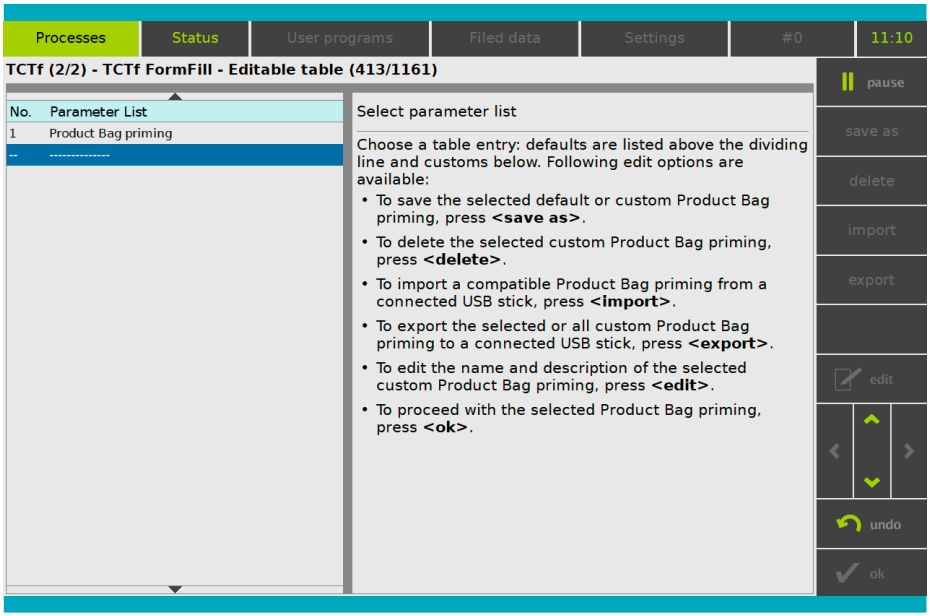
IMPORTANT

If a Product Bag is not primed at this stage, it cannot be primed later.

The priming process of product bags starts. It is essential to prime the surfaces in the bags with formulation solution and to remove all air bubbles from the bags.



Screen 8.51: Product Bag priming



Screen 8.52: Select parameter list.

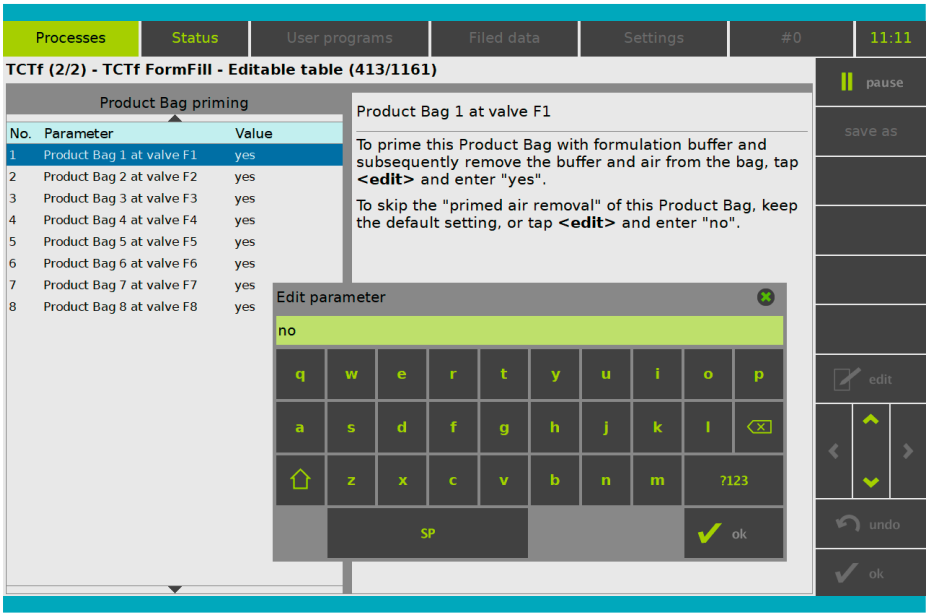
Which Product Bags are primed can be decided in an editable table. After choosing a priming table, a new window with the actual table is shown. To adjust the selection of Product Bags for priming, tap <edit> and then enter <yes> or <no> with the keyboard (see Screen 8.53).

- <yes>: the bag will be primed with formulation solution and can be used for drug product filling.
- <no>: the bag will not be primed and will not be available for drug product filling.

At least one Product Bag has to be chosen for priming to continue. It is recommended to prime all Product Bags.

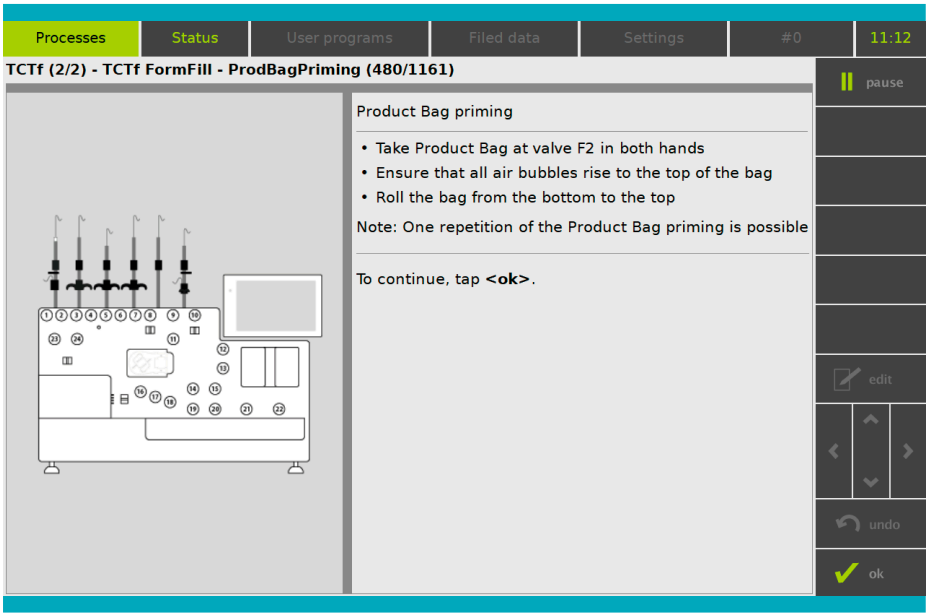
The user can create individual priming tables which remain can be saved on the instrument. For detailed instructions, tap the dividing line (<-- ---------->) in the list on the left-hand side of the screen (see Screen 8.52). To create an individual priming table, select a default table as a template (“Product Bag priming”) and tap <save as>.

Rename the new activity matrix with maximal 30 digits (e.g., “Individual protocol 1”) and give it an individual description with maximal 300 digits. Special characters are not allowed. To edit an existing priming table, select it from the list and tap <edit>. Including the default table up to 50 priming tables can be saved on the instrument concurrently. The protocols are serially numbered in the list. To edit or delete newly created priming tables tap <edit> or <delete>.



Screen 8.53: Select bags to be primed.

When the selection of a Priming table was made, tap <ok> to continue. Priming of the chosen bags starts. Follow the instructions given on the screen.



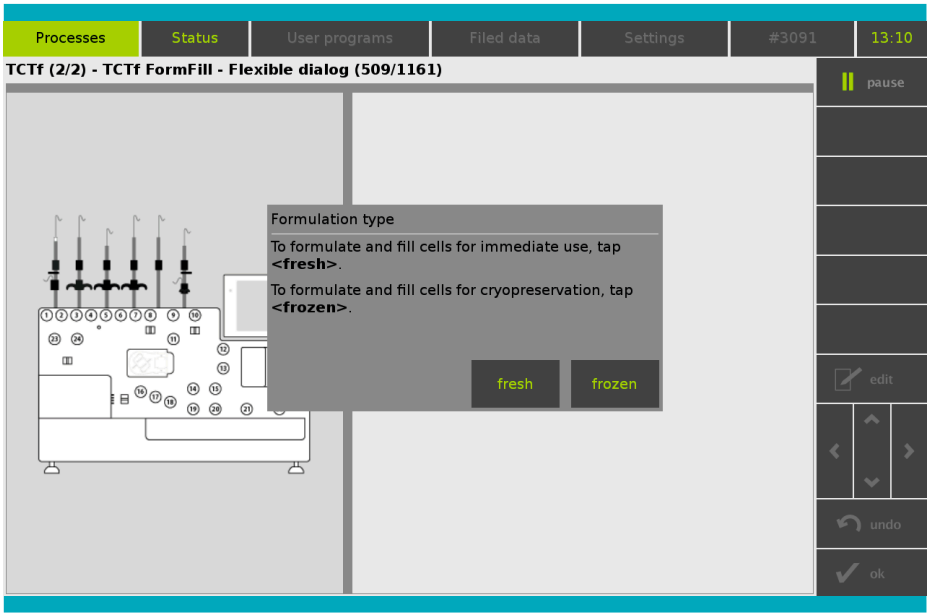
Screen 8.54: Instructions for priming of product bag

It is essential to remove all air bubbles from the bags. If necessary, retry is possible once per bag. Large bags (1–4) are initially filled with 40 mL of formulation solution and 20 mL on retry, while smaller bags (5–8) receive 20 mL in both instances.

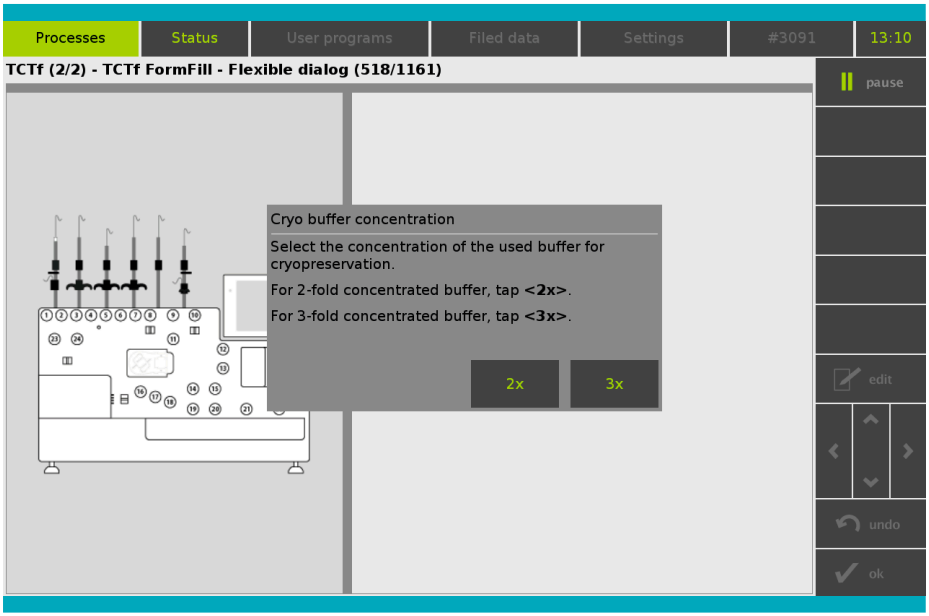
During the priming the cells are stored in the chamber at 8 °C (46 °F) with slow shaking.

Preparation of formulation:

After priming, choose between the two formulation types fresh or frozen and confirm (see Screen 8.55). If frozen is selected, select 2× or 3× cryo concentration based on the fold concentration of your cryo preservation solution (see Screen 8.56).



Screen 8.55: Select fresh or frozen option



Screen 8.56: Select cryo buffer concentration

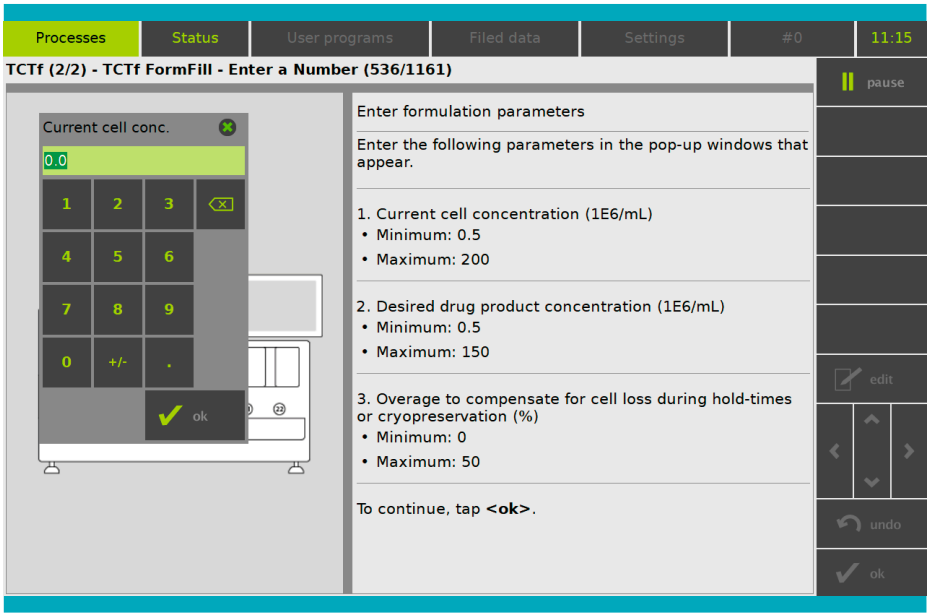
IMPORTANT

It is recommended to keep two QC Bags for the formulation and filling process. At least one QC Bag is necessary.

Enter the values for current cell concentration, desired drug product concentration, and overage from the sample testing according to the ranges shown on the screen. Every entered value below 0.5 will be rounded automatically to 0.5 for calculation (see Screen 8.57).

Make sure that the current cell concentration and the desired drug product concentration refer to the same target cell type (e.g. $CD3^+$ cells or CAR^+ cells).

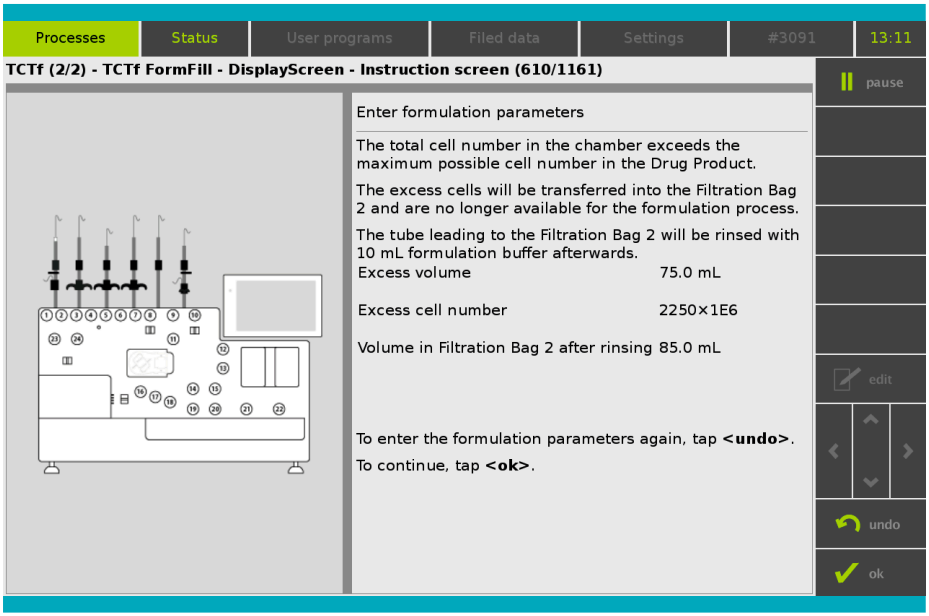
The overage will increase the formulated drug product concentration to compensate a potential or known percentage of cell loss during hold-times or cryopreservation.



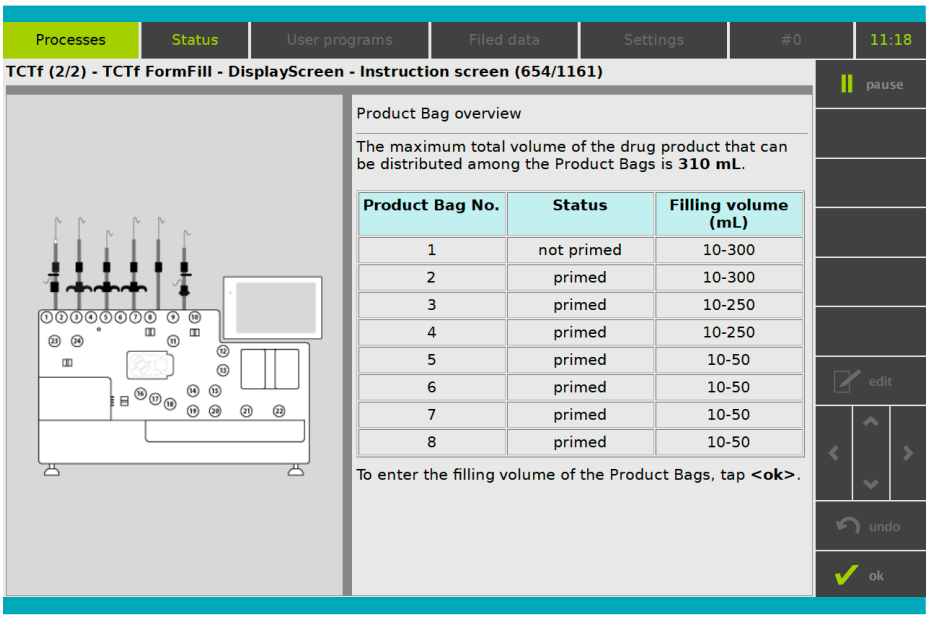
Screen 8.57: Enter formulation parameters.

The instrument calculates the drug product volume which can be filled in Product Bags and shows it on the screen together with an overview of the priming status of the Product Bags (see Screen 8.59). Only primed Product Bags are available for filling with drug product.

In case excess volume has to be removed from the chamber during the formulation, the excess volume will be transferred to the Filtration Bag 2 and the excess volume and excess cell count will be displayed on the screen.



Screen 8.58: Excess volume



Screen 8.59: Product bag volume and filling volumes.

The Product Bag overview shows the priming status of the Product Bags together with their allowed filling volume ranges (see Screen 8.59). Use this information to decide how the available drug product should be distributed on the available bags. To enter the volume(s), tap <ok>.

IMPORTANT
Note down the drug product volume shown on the screen for your reference.

Preparation of filling

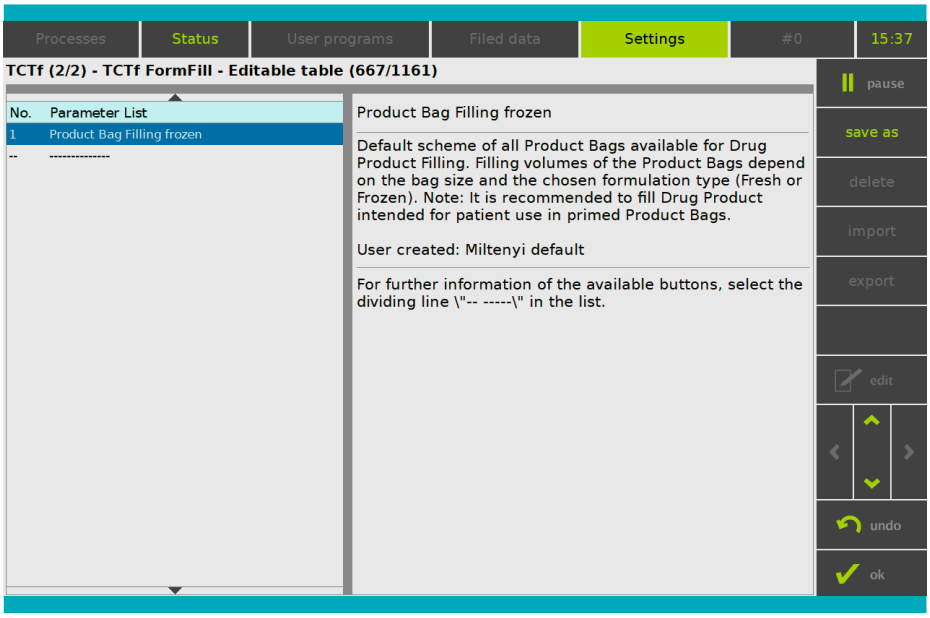
Which Product Bags are filled with which volume can be decided in an editable table. After choosing a filling table, a new window with the actual table is shown. To adjust the filling volumes of the bags, tap < edit > and then enter the desired volume with the keyboard shown on the screen.

The user can create individual filling tables which can be saved on the instrument. For detailed instructions tap the dividing line (<-- ---------->) in the list on the left-hand side of the screen (see Screen 8.60). To create an individual filling table, select a default table as a template ("Product Bag filling fresh" or "Product Bag filling frozen") and tap <save as>. Rename the new filling table with maximal 30 digits (e.g., "Individual protocol 1") and give it an individual description with maximal 300 digits. Special characters are not allowed.

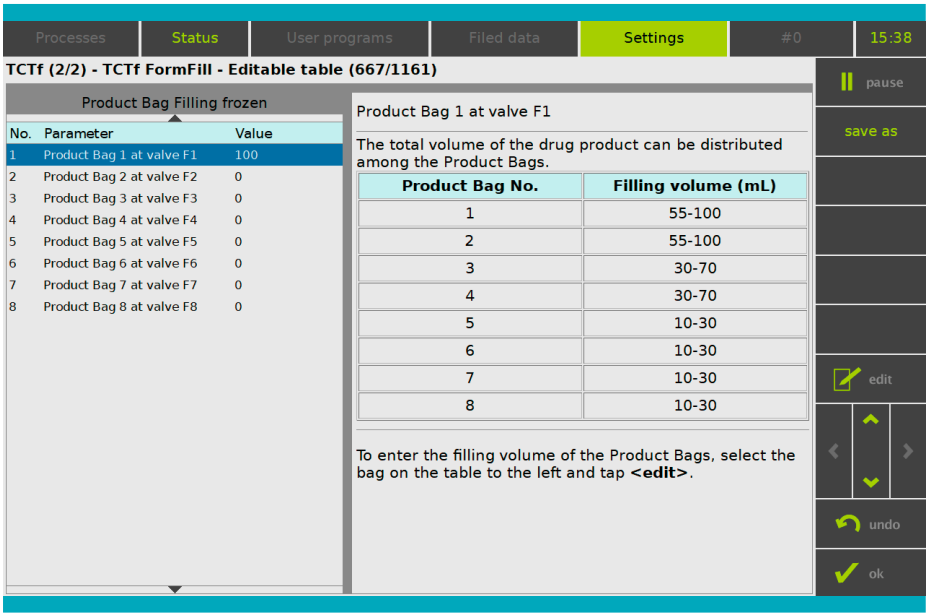
To edit an existing filling table, select it from the list and tap <edit>. Including the default table up to 50 filling tables can be saved on the CliniMACS Prodigy concurrently. The protocols are serially numbered in the list. To edit or delete newly created filling tables tap <edit> or <delete>.

To save adjusted tables, tap <save as>.

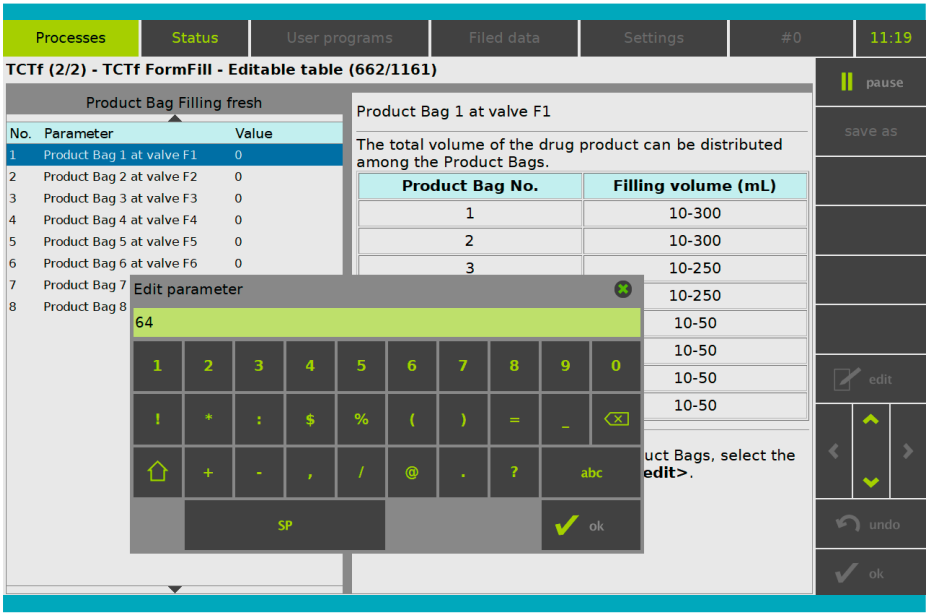
IMPORTANT
If all Product Bags were chosen for filling with the drug product, the residual drug product volume will automatically stay in the chamber.



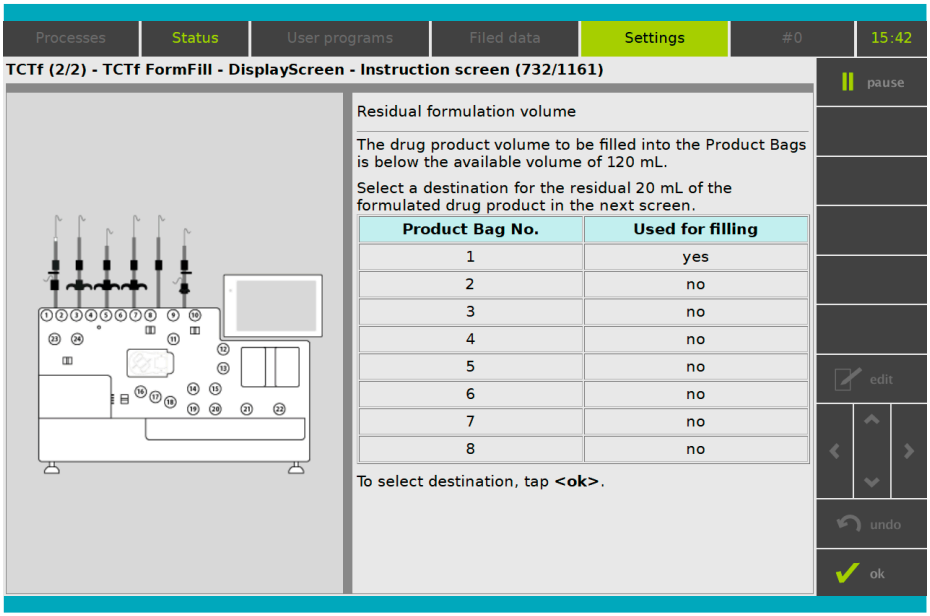
Screen 8.60: Product Bag filling



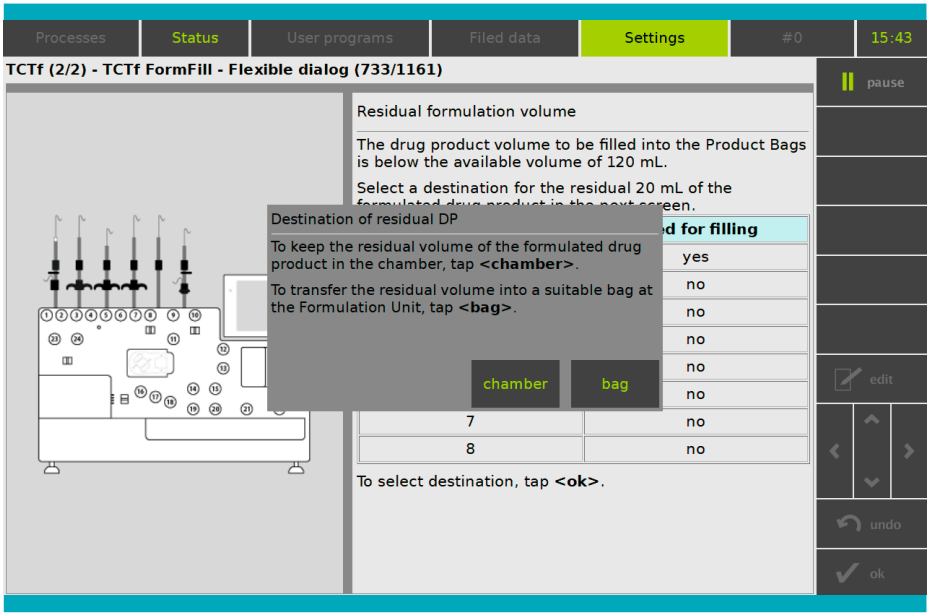
Screen 8.61: Filling table



Screen 8.62: Edit filling table



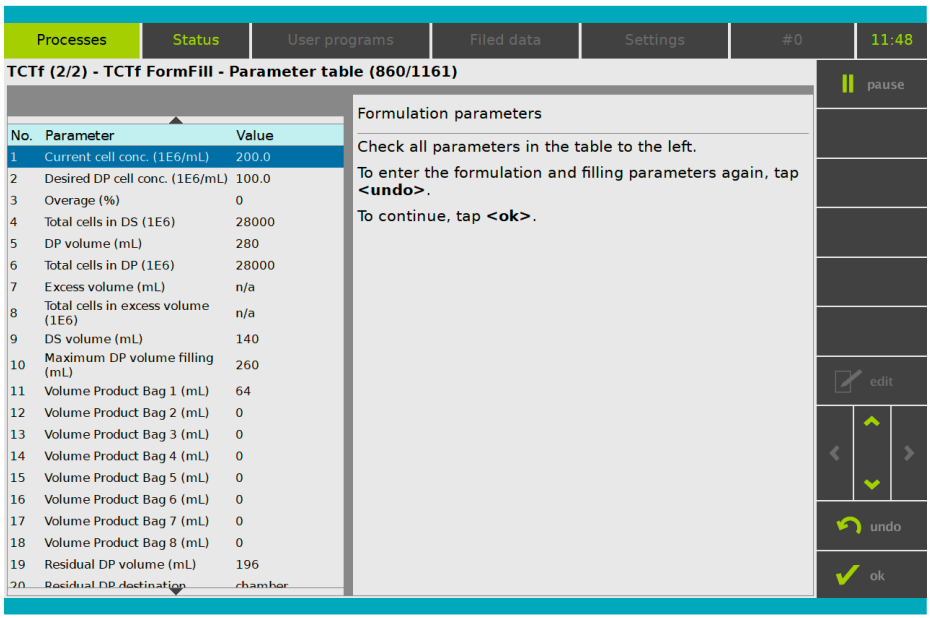
Screen 8.63: Residual formulation volume



Screen 8.64: Select destination for residual formulation volume

In case not the whole available drug product volume is used for filling, the process will show the residual volume on the screen. The process offers the choice to select a free Product Bag for the residual volume or to leave it in the chamber.

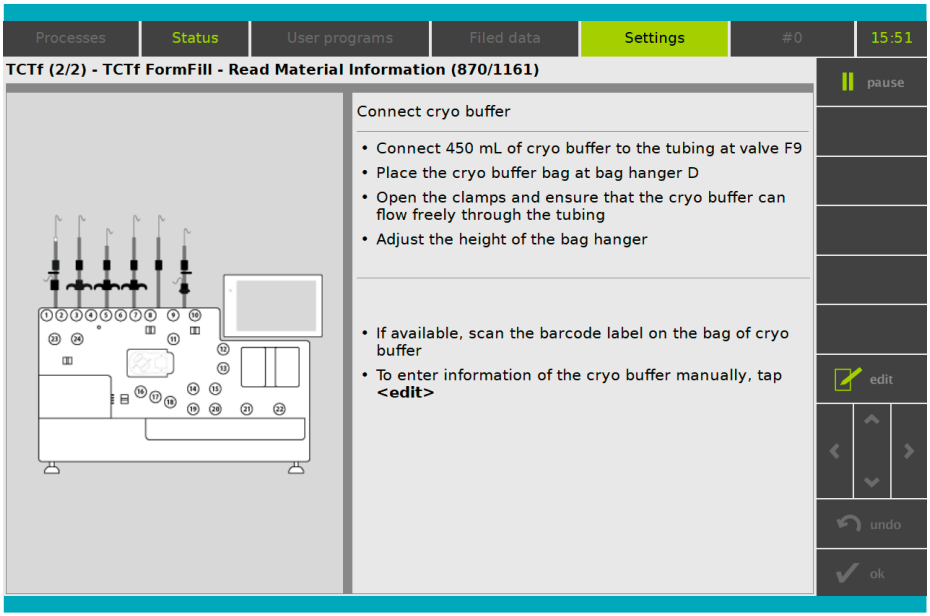
A summary of the given formulation and filling parameters is shown (see Screen 8.65).



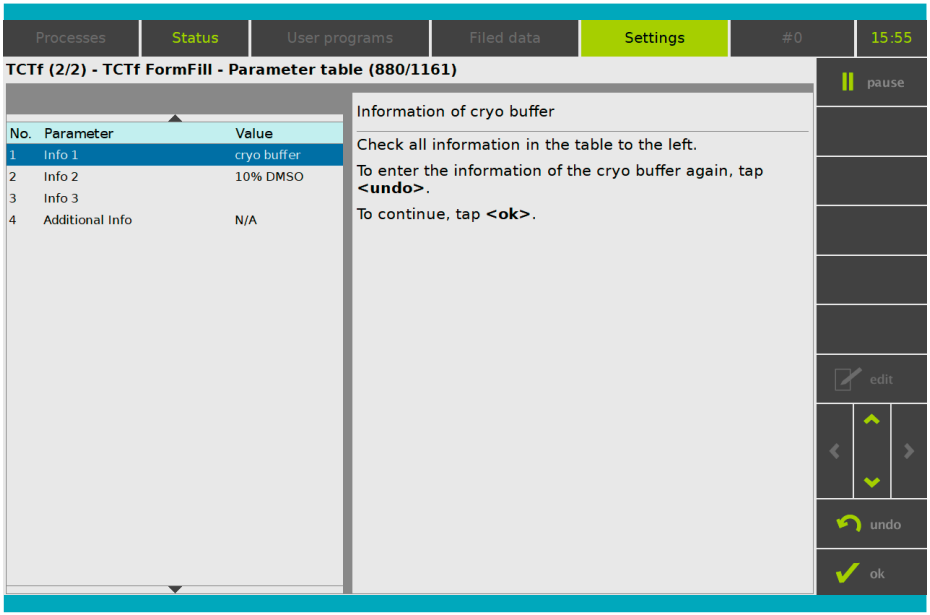
Screen 8.65: Formulation parameters

To continue the formulation and filling, tap <ok> and then confirm.

In case formulation type frozen was chosen, connect the cryo buffer now as shown on the screen (see Screen 8.66). Read the barcode label on the cryo buffer bag. To manually enter the information, tap <edit>, then tap <ok>.



Screen 8.66: Connect cryo buffer

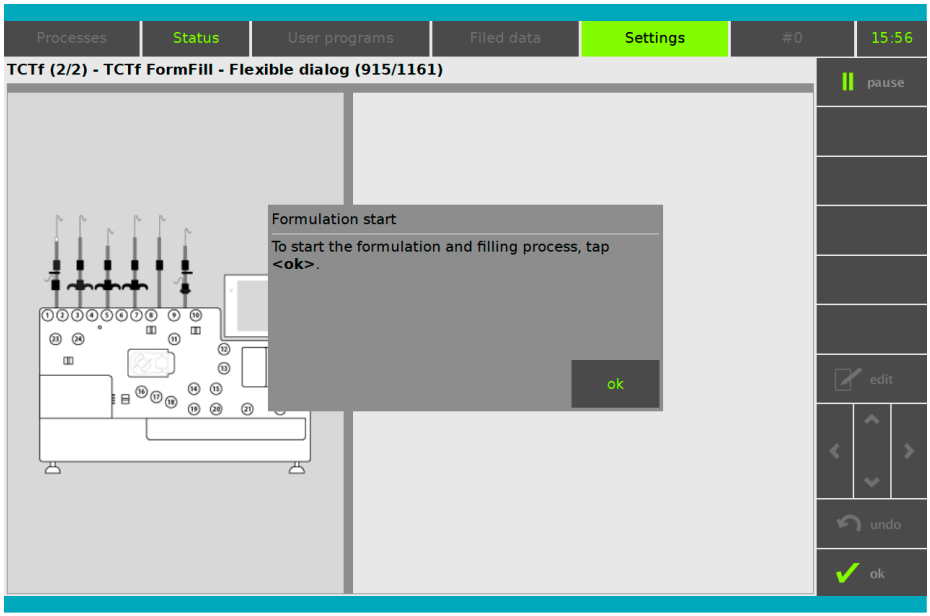


Screen 8.67: Information on cryo buffer

The input for the cryo buffer is summarized (see Screen 8.67).

Formulation and filling

A pop-up about formulation start will open. To start the formulation and filling process, tap <ok> in the pop-up (see Screen 8.68).



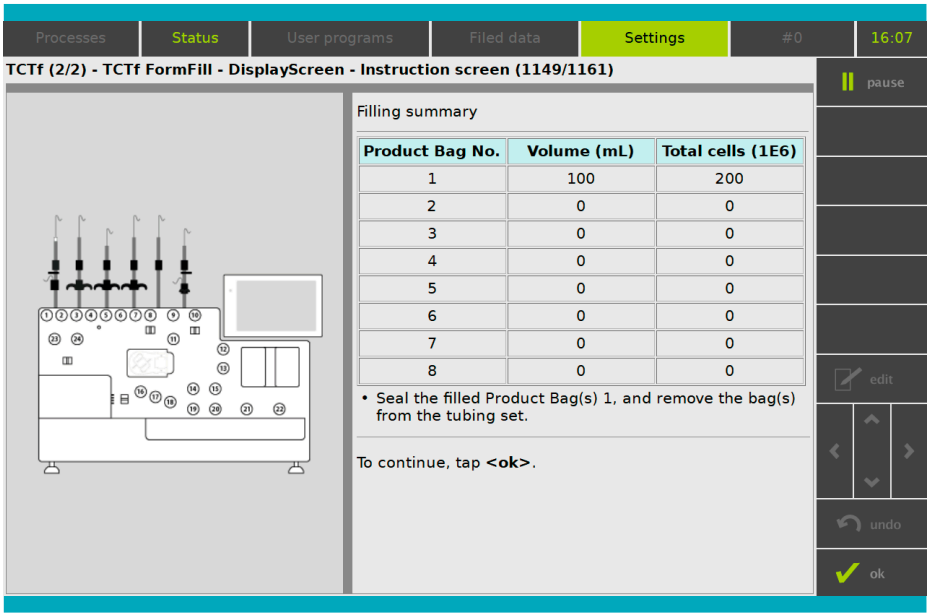
Screen 8.68: Formulation start

The formulation and filling procedure will be performed completely automated and does not require user interaction until finalized.

The process will automatically adjust the cells in the chamber to the desired cell concentration, in the previously shown drug product volume. In case of frozen formulation the cryo buffer will be added at the end of the formulation procedure.

When the cells are formulated in the desired concentration the process starts to fill the Product Bags according to the filling table with the desired volumes. In case several Product Bags will be filled, the filling will always proceed in the order from Product Bag 1 to Product Bag 8. In case a bag was chosen for the filling of residual drug product volume, this bag will be filled last.

At the end of the formulation and filling process, a summary filling table is shown, listing the filled Product Bags with filling volumes and the containing cells.

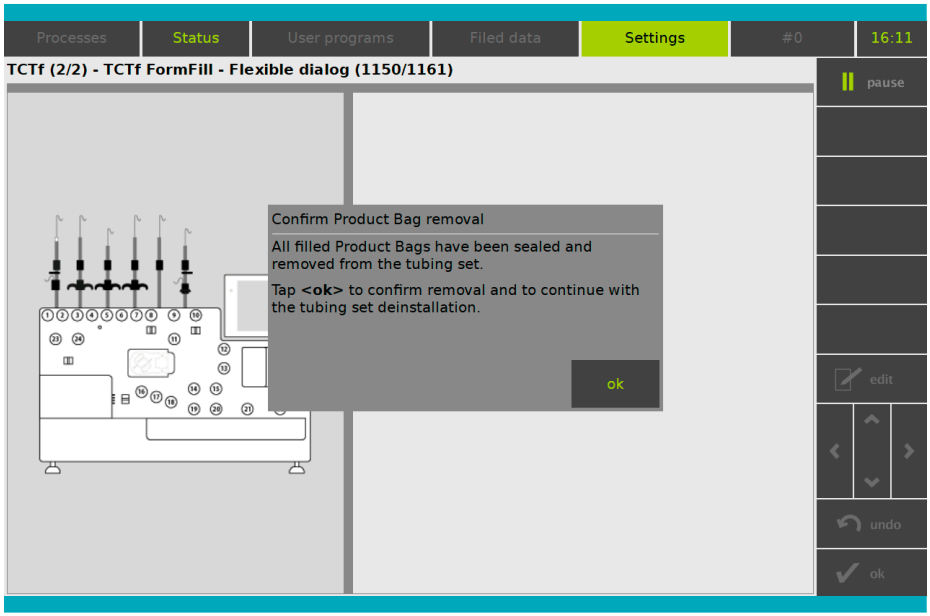


Screen 8.69: Filling summary

Follow the instructions on the screen to remove the filled Product Bags from the tubing set using the tube sealer. To continue tap <ok>.

To confirm the successful removal of the Product Bags in the pop-up (see Screen 8.70), tap <ok>.

The time of confirmation will be tracked in the process specific protocol and can be used to calculate e.g. the contact time of the cells with dimethyl sulfoxide (DMSO).

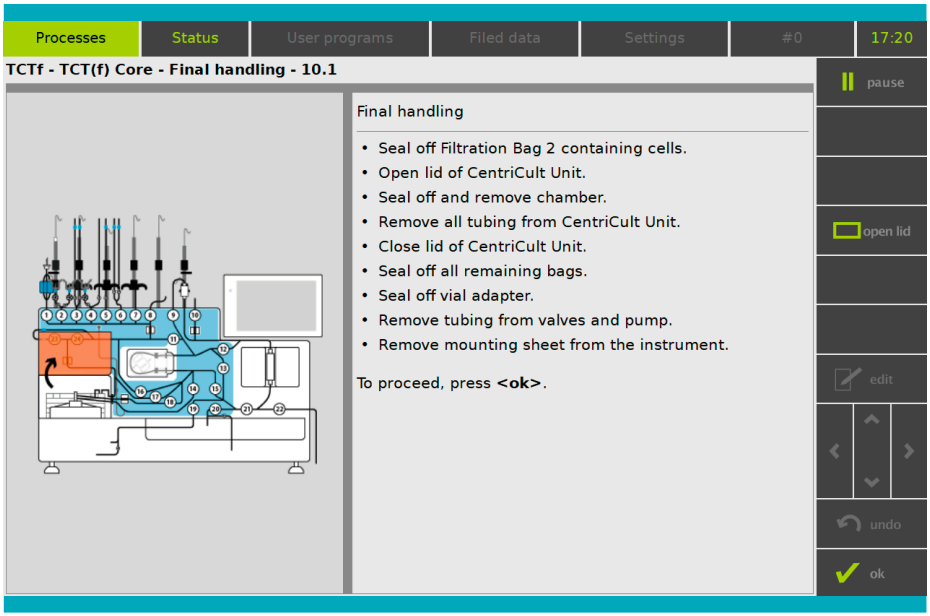


Screen 8.70: Confirm Product bag removal

8.5 Final handling

8.5.1 Final handling after end of culture type 1 and 2

After termination of the process, the program guides through the final handling steps (see Screen 8.71).



Screen 8.71: Final handling in end of culture type 1 and 2

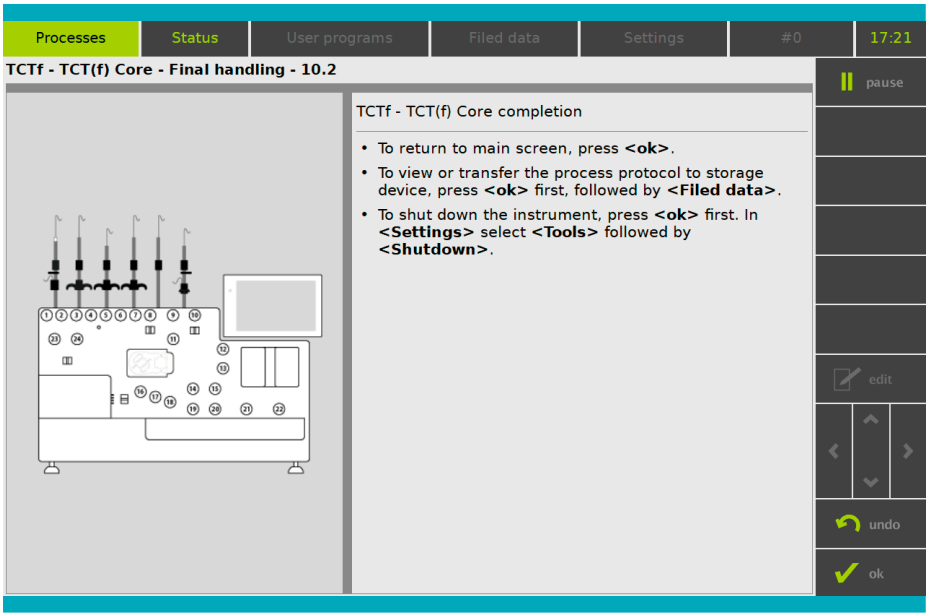
Seal off the Filtration Bag 2 on valve 10 containing the cell product. Take a sample from the Filtration Bag 2 for further analysis, using the QC pouch. Store samples at +4 to +8 °C (+39 to +46 °F).

If no cultivation was performed and the final handling takes place directly after enrichment (see section 7.6.2 ´Completion of enrichment process´), seal off the Reapplication Bag containing the enriched target cells. If required, take a sample from the Reapplication Bag, using the QC pouch, for further analysis.

Follow the instructions given on the screen to remove the tubing set and to finalize the process (see Screen 8.71). The lid of the CentriCult Unit unlocks automatically during this process step. If the lid does not unlock automatically, tap <open lid> on the menu bar. In the event the lid cannot be opened, contact Miltenyi Biotec Technical Support.

Important
Dispose of the tubing set as biohazardous material according to the standard operating procedures of the institution. Consider the genetic engineering biosafety level of the used viral vector for waste disposal.

After removal of the tubing set the process is completed (see Screen 8.72).

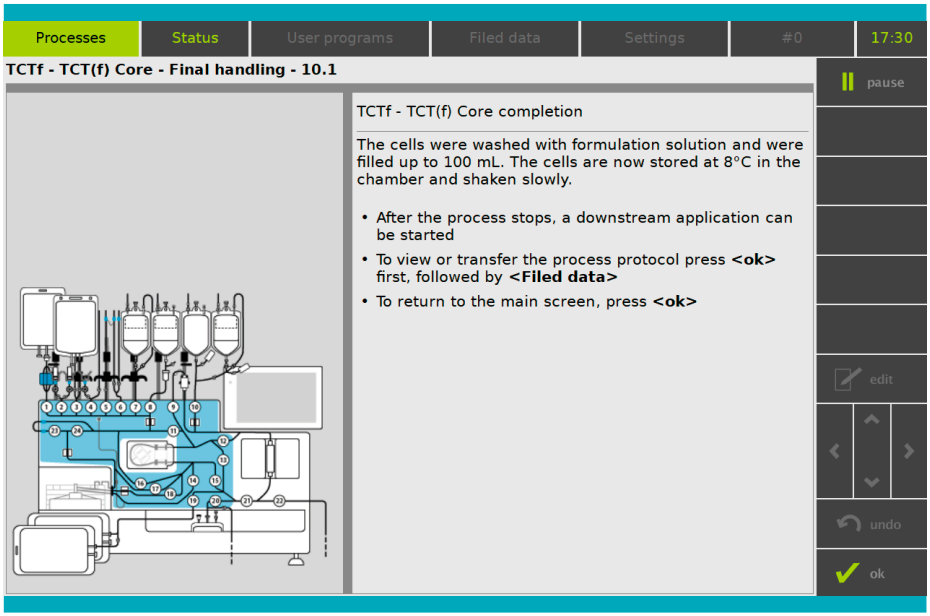


Screen 8.72: Process completion after end of culture type 1 and 2

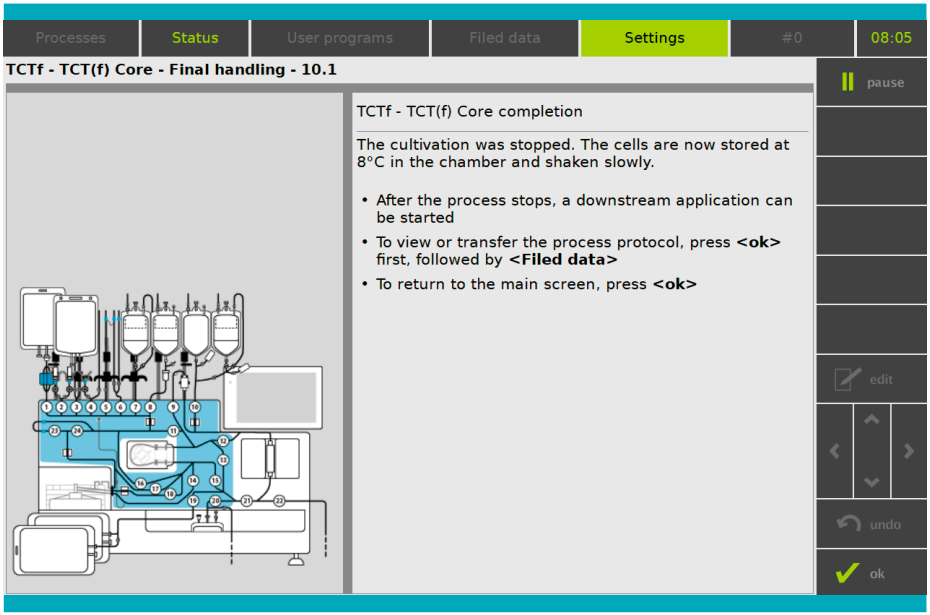
8.5.2 Final handling after end of culture type 3 and 4

After end of culture type 3 and 4 cells remain in chamber at 8 °C (46 °F) with slow shaking.

During this time, preparations for downstream processes should be performed.



Screen 8.73: Process completion after end of culture type 3

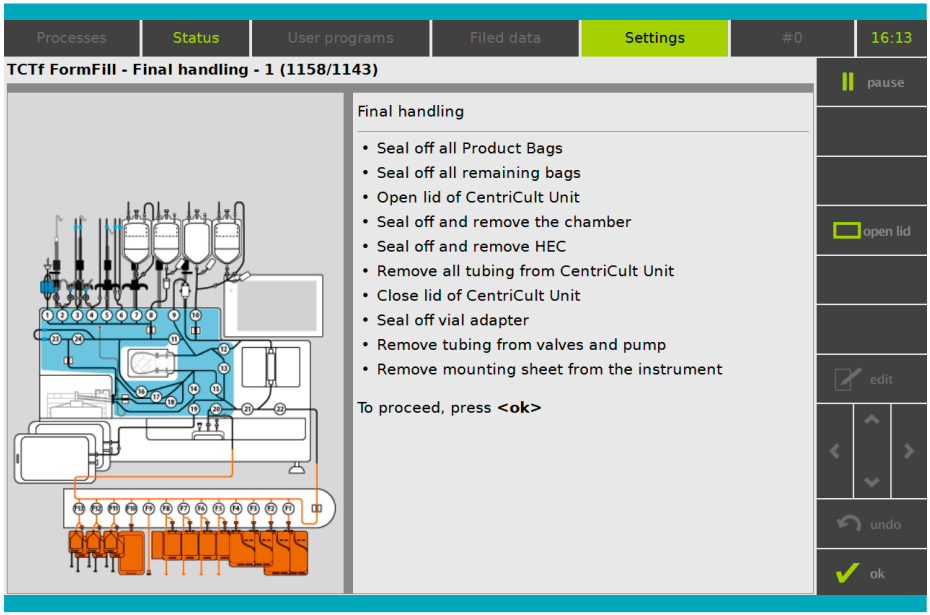


Screen 8.74: Process completion after end of culture type 4

To stop the temperature control and shaking, tap <ok> (see Screen 8.73 and Screen 8.74).

After completing the process, the CliniMACS Prodigy can then be used for a (customized) downstream process using the same CliniMACS TS 521.

8.5.3 Final handling after end of culture type 5

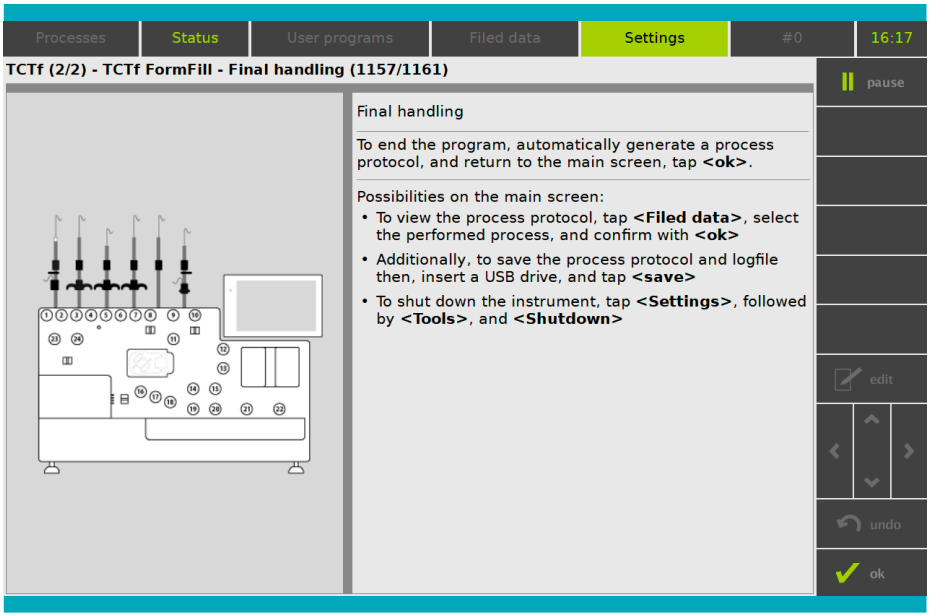


Screen 8.75: Process completion after end of culture type 5

Seal off and remove the bags, which should be kept, e.g., excess volume in Filtration Bag 2, and follow the instructions for the tubing set removal (see Screen 8.75).

Follow the instructions given on the screen to remove the tubing set.

To continue and finalize the process, tap <ok>.



Screen 8.76: TCTf FormFill process completion

8.5.4 Download of process log files

The process protocols are stored in <Filed data> and can be transferred to other media with a standard USB flash drive. To do so, plug an USB flash drive into the USB port located at the side of the touch screen. Tap <Filed data> on the menu bar and select the requested process. Then tap <save> to transfer the process protocol to the USB flash drive.

Be aware that for the full TCTf process, including end of culture type 5, four individual protocols will be generated, TCTf, tctf_core, TCTf_FormFill, and TCTf_ results.

The protocol "tctf_core" contains all the process information, except for information about the activity end of culture type 5. In case end of culture type 5 was executed, the protocol "TCTf_FormFill" contains the according information about this activity.

8.5.5 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.

8.5.6 Cleaning and disinfection

Clean and disinfect the CliniMACS Prodigy 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 institution's standard procedures for the treatment of infectious materials.

8.5.7 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.

All QC samples should be analyzed according to standard operating procedures. For the manufacture and use of the engineered T cells, national and international legislation and regulations must be followed.

Miltenyi Biotec as the provider of the CliniMACS Prodigy T Cell Transduction and Automated Formulation 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.

9 Troubleshooting

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

+49 2204 8306-3803
technicalsupport@miltenyi.com

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

10 Legal notes

9.1 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.

For products purchased from third-party retailers or resellers (e.g., purchased from an Authorized Distributor of Miltenyi Biotec), different terms and conditions may apply.

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.

Miltenyi Biotec's warranty does not cover products sold AS IS or WITH ALL FAULTS or consumables. Nothing herein should be construed as constituting an additional warranty.

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
Miltenyi Biotec shall not be liable for any incidental or consequential damages for breach of any express or implied warranty or condition on this product.

Some countries/states or jurisdictions do not allow the exclusion or limitation of incidental or consequential damages, so the above limitations or exclusions may not apply to you. This warranty statement gives you specific legal rights and you may have other rights, which vary from state to state or jurisdiction to jurisdiction.

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