Miltenyi Biotec

CliniMACS Prodigy® Hematopoietic Stem Cell Transduction – Large Scale System

User manual

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



The CliniMACS System components, including Reagents, Tubing Sets, Instruments, and PBS/EDTA Buffer, are designed, manufactured and tested under a quality system certified to ISO 13485. In the EU, the CliniMACS System components are available as CE-marked medical devices for their respective intended use, unless otherwise stated. In the US, the CliniMACS CD34 Reagent System, including the CliniMACS Plus Instrument, CliniMACS CD34 Reagent, CliniMACS Tubing Set TS and LS, and the CliniMACS PBS/EDTA Buffer, is FDA approved as a Humanitarian Use Device (HUD), authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this indication has not been demonstrated. Other products of the CliniMACS Product Line are available for use only under an approved Investigational New Drug (IND) application or Investigational Device Exemption (IDE) or FDA approval.
MACS GMP Products and 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®
Hematopoietic Stem Cell Transduction – Large Scale System

User manual

Process version 1.x

Issued: 2026-02

210-005-784/01

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1

About the manual

This user manual provides information for the use of the CliniMACS Prodigy Hematopoietic Stem Cell Transduction – Large Scale (HSCT-LS) System. For further details on other processes running on the CliniMACS Prodigy, refer to the CliniMACS Prodigy Instrument 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 cellular starting products are described in the CliniMACS Prodigy Instrument user manual. For instructions for use, for example warnings and precautions, concerning the CliniMACS Prodigy HSCT-LS 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 users 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 3.2 ´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 must 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.

1.3.1 Text styles

• Bullet point list item with text	Indicates a list item
1. Numbered list item with text	Indicates a list item of a step-by-step instruction
Bold < colored > text	Indicates software elements, for example, a button or a tab of the user interface
See section 1.3.1 ´Text styles´	References to the section with the number 1.3.1 and the heading ´Text styles´
See Figure 2.1/Screen 2.1/Table 2.1	References to the first figure/screen/table in the second chapter

IMPORTANT
Advises the user of important practices or information not related to personal injury nor property damage.

1.3.2 Screens and figures

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

1.3.3 Warning messages

The following examples show the layout of warning messages at the beginning of a chapter/section where a hazard can occur. The level, type, and source of the hazard, as well as potential consequences, prohibitions, and measures are indicated as follows. The color and signal word of a warning message depend on the hazard level (see chapter 3.1 ´Hazard levels´).

⚠ 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 examples show the layout of embedded warning messages which provide safety information within instructions or other text:

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.

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 Instrument user manual. The glossary of symbols depicts the symbols used for labeling of the CliniMACS® Products.

3

Warnings and precautions

3.1 Hazard levels

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

⚠ WARNING

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

⚠ CAUTION

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

NOTICE

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

3.2 General safety instructions

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 material are described in the CliniMACS Prodigy Instrument user manual.

For instructions for use, for example warnings and precautions, concerning the CliniMACS Prodigy HSCT-LS System components, refer to the instructions for use provided for the respective component.

4 Introduction

4.1 General information

Hematopoietic stem cells (HSCs) can be stably modified by introduction of genetic material using viral vectors. For example, viral transduction allows the introduction of a functional copy of an affected gene into a diseased HSC to restore its normal function.

The generation of gene-modified HSCs requires sequential steps consisting of cell cultivation and transduction.

The CliniMACS Prodigy HSCT-LS System allows the entire process, including formulation of the product, to be performed in an automated and closed system (see Figure 4.1). Samples for quality control (QC) can be obtained during manufacturing using sterile technique.

The components that are required to perform the HSC engineering with the CliniMACS Prodigy HSCT-LS System are described in detail in chapter 5 ´Materials required´.

This user manual provides guidance for the use of the CliniMACS Prodigy HSCT-LS System in order to manufacture gene-modified HSCs for clinical application.

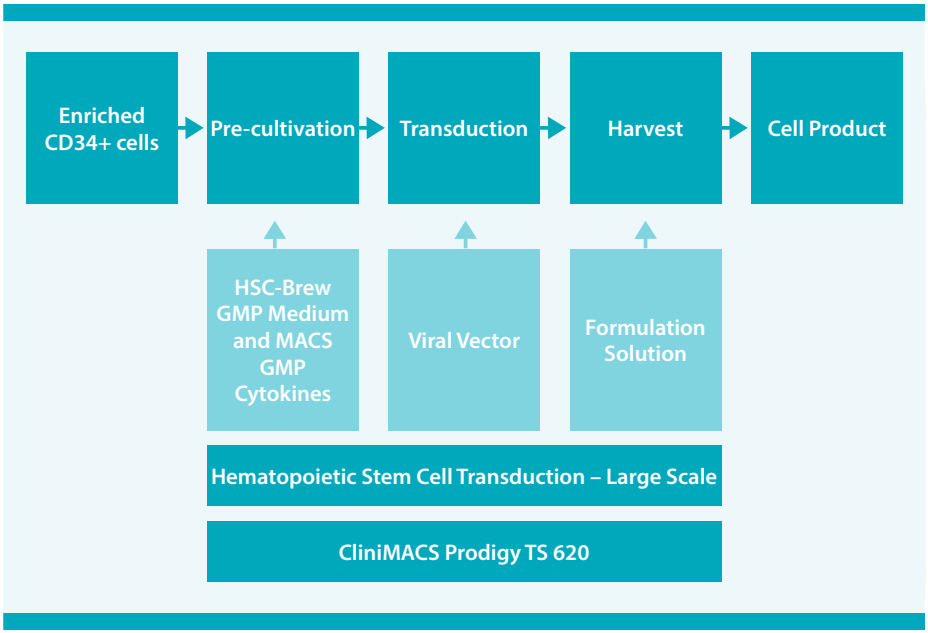


Figure 4.1: Generic manufacturing scheme using the CliniMACS Prodigy HSCT-LS System

IMPORTANT
This user manual describes the full process and includes a recommended protocol. In order to ensure a high-quality cell product, Miltenyi Biotec recommends using the cytokines and media as described in this user manual.

4.2 Process overview

The CliniMACS Prodigy HSCT-LS System enables the cultivation and gene modification of HSCs by viral transduction. It is comprised of the CliniMACS Prodigy, CliniMACS Prodigy Tubing Set (TS) 620, HSC-Brew GMP Medium, and MACS® GMP Cytokines such as stem cell factor (SCF), thrombopoietin (TPO) and Fms-related tyrosine kinase 3 ligand (Flt3-Ligand).

At the beginning, two options are available (see Figure 4.2): "Full process" (Case 1) or "Resume cases" (Case 2). The latter has 2 subcases: Case 2.1 "Resume HSC cultivation" or Case 2.2 "Resume end of culture".

Full process

Case 1: "Full process" is chosen to run the full process, including tubing set installation, integrity test, tubing set priming and cultivation.

Resume cases

A resume case is used if the HSCT-LS process was interrupted and the cells are already in the chamber.

Case 2.1: "Resume HSC cultivation" starts directly with the setup of the HSCT-LS System protocol.

Case 2.2: "Resume end of culture" can be used to continue with one of four different end of culture options.

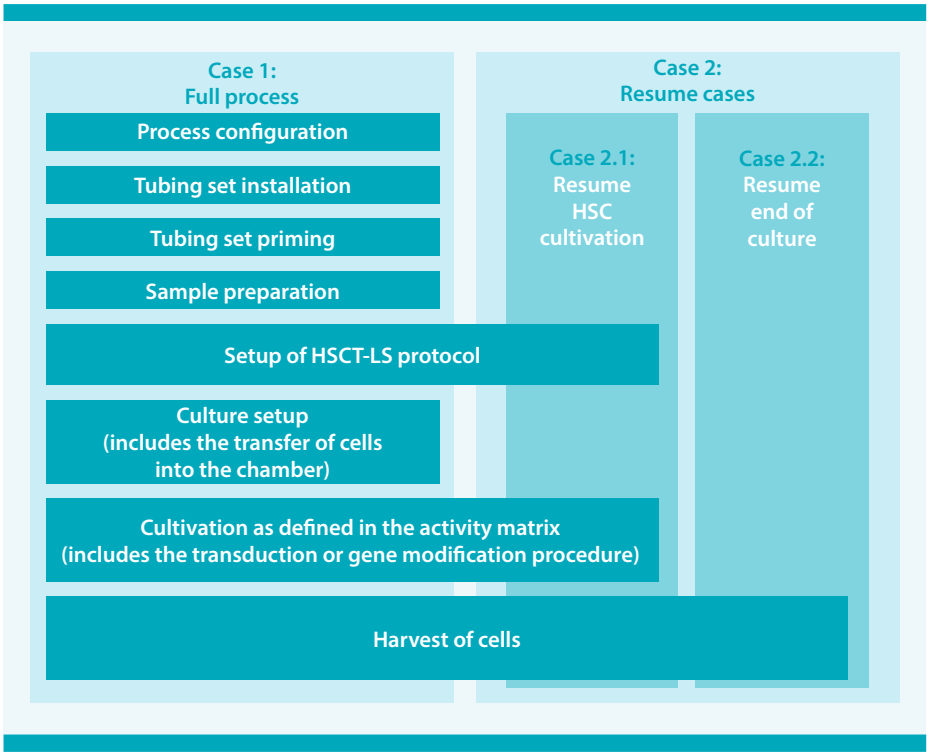


Figure 4.2: General overview of the CliniMACS Prodigy HSCT-LS process

This user manual describes the complete process (option 1 “Full process”) listed as general overview here:

- Installation of the CliniMACS Prodigy TS 620 on the instrument.
- Connection of the HSC-Brew GMP Medium on valve 3 (from here on termed medium).
- Priming of CliniMACS TS 620 with medium.
- Connection of the HSC Brew-GMP Medium containing MACS GMP Cytokines on valve 4 (from here on termed medium with cytokines).
- Connection of the cellular starting material containing CD34+ cells on valve 8 (from here on termed cell bag).
- Transfer of cells into the chamber including the addition of medium with cytokines and washing steps if desired.
- Start of cultivation including warming and gas supply.
- Execution of the previously defined protocol (from here on termed activity matrix) including the transduction with the connection of the bag containing the viral vector (from here on termed transduction reagent bag).
- Harvest of the genetically-modified cells.
- After harvest, the final cell product is ready for further processing.

General information:

- The activity matrix is a flexible protocol which is composed of individual steps (termed activities) such as transduction, gene modification, volume reduction, feeding with medium containing cytokines, and chamber shaking, among others. These activities will be executed as defined by the user and can be edited during the cultivation process.
- The status of the process can be monitored on the screen of the instrument and all manual handling steps are guided by the graphic user interface (GUI) and this user manual.
- Culture monitoring and QC can be performed using the available microscope and sampling functions.

IMPORTANT
The CliniMACS Prodigy HSCT-LS System has a maximum capacity with respect to cell transduction. Details are described in section 6.1 ´Preparation of cellular starting material´.

5
Materials required

The following section outlines the materials and consumables required for the generation of gene modified HSCs with the CliniMACS Prodigy HSCT-LS System.

5.1 System components

The following components are recommended for the CliniMACS Prodigy HSCT-LS System (see Table 5.1).

Material	Quantity	Required for case(s)	Comments
CliniMACS Material			
CliniMACS Prodigy	1	All[A]	
CliniMACS Prodigy TS 620	1 set	All[A]	
MACS GMP Materials			
HSC-Brew GMP Medium	Up to 2 L	All[A]	
MACS GMP Recombinant Human SCF	2×10^5 *U*	All[A]	Specific amount depends on the lot-specific activity (*U*/mg). Refer to the package insert and the Certificate of Analysis.
MACS GMP Recombinant Human Flt3-Ligand	1.44×10^5 *U*	All[A]	Specific amount depends on the lot-specific activity (*U*/mg). Refer to the package insert and the Certificate of Analysis.
MACS GMP Recombinant Human TPO	8×10^5 *U*	All[A]	Specific amount depends on the lot-specific activity (*U*/mg). Refer to the package insert and the Certificate of Analysis.
Software			
HSCT-LS Process (process version V1.0)			

A For all resume cases (case 2.1 and 2.2) be aware that the required material has 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 5.1: Components recommended for the CliniMACS Prodigy HSCT-LS System for a one-hit transduction in a 100 mL cultivation without stage load during culture setup ending in end of culture type 1

IMPORTANT

The materials referenced above are recommended for the use in combination with the HSCT-LS process. The user is responsible for the validation of the process.

5.2 Additional materials required

Besides the components listed in Table 5.1, additional materials are required for the HSCT-LS process (see Table 5.2).

Material	Comment
Biological materials	
Enriched CD34+ cells	• Minimum of 2×10^7 CD34+ cells • 40 – 2280 mL
Sterile water	Pharmaceutical grade
Viral vector	10 mL recommended
Formulation solution	1 L e.g., physological sodium chloride solution with 0.5% HSA
Human serum albumin (HSA)	Use only pharmaceutical grade HSA approved in your country
Consumables	
Syringes	• 0.5 mL, several • 1 mL, several • 10 mL, several • 50 mL, several
Hypodermic needles	20 gauge, several
Disposable bags	At least 1 bag, e.g., 150 mL, depending on application. The bags must be connectable to the tubing set via welding.
Luer/Spike Interconnector	At least 1 piece, depending on application. Only required in case disposable bags have no Luer lock port for the connection of syringes.
Triple Sampling Adapter	If more than 3 in-process controls are required during cultivation
3-way Tube Adapter	1 piece (depending on culture volume and the protocol)
1 m Tube Extension	1 piece
Reagent bag	20 mL
Equipment	
Uninterruptable power supply	
CO_2 and compressed air supply	
Sterile tubing welder, e.g., Terumo Sterile Connecting Device	

Table 5.2: Materials recommended for the CliniMACS Prodigy HSCT-LS System for a one-hit transduction in a 100 mL cultivation without stage load during culture setup ending in end of culture type 1

IMPORTANT

This protocol requires the use of components and materials which are not part of the CliniMACS Prodigy HSCT-LS System, for example human serum albumin. Use only pharmaceutical grade HSA approved in your country. 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. Carefully read the package insert of the HSA used, particularly the section regarding hypersensitivity reactions and the risk of infection associated with HSA as a blood-derived product. Evaluate all risks arising from this material.

6 Preparative steps

The gene modification of HSCs using the CliniMACS Prodigy HSCT-LS System is an automated process and requires a few preparative steps. The following section describes the preparation of the cellular starting material, the medium, the cytokines and the transduction reagent.

⚠ 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 (for example laminar flow hood) using aseptic techniques.

6.1 Preparation of cellular starting material

The CliniMACS Prodigy HSCT-LS System can be used to introduce genetic material into previously enriched CD34+ cells. Human HSCs are positive for the cell surface marker CD34 and can be enriched for example from mobilized leukapheresis by using the CliniMACS Plus or the CliniMACS Prodigy.

Before starting the process, determine the volume and the cell concentration of the cellular starting material. It is recommended to start with a total cell number of at least 2×10^7 CD34+ cells. The minimum volume of cellular starting material is 40 mL, the maximum volume 2280 mL. In case the separated CD34+ cells are not present in a bag, transfer the cellular starting material into a bag (termed cell bag) which can be connected to the tubing set by sterile welding.

IMPORTANT

If it is required to start with less than 2×10^7 CD34+ cells or less than 40 mL culture volume contact Miltenyi Biotec Technical Support.

⚠ 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 cellular starting material to be processed.

6.2 Preparation of medium

Depending on the transduction protocol (for example number of transduction rounds and culture volume) 1.5 to 4 liters HSC-Brew GMP Medium are required.

- Prepare the HSC-Brew GMP Medium as described in the package insert. The complete HSC-Brew GMP Medium is hereafter referred to as "medium" and the bag as "medium bag".
- Refer to section 7.4.1 ´Connection of medium´ on connecting the medium to the tubing set.

Contact Miltenyi Biotec Technical Support for a detailed calculation of the media consumption.

6.3 Preparation of medium with cytokines

The MACS GMP Recombinant Human Cytokines SCF, Flt3-Ligand and TPO (hereafter collectively called cytokines) are not part of the medium and must be added separately. In the following chapters the reconstitution of cytokines and the preparation of the medium bag with cytokines are described.

6.3.1 Reconstitution of cytokines

The biological activity of the cytokines is lot-specific and indicated on the respective Certificate of Analysis. Reconstitute each cytokine as described in the package insert to prepare a cytokine stock.

6.3.2 Addition of cytokines to the medium

After reconstitution of cytokines, the medium bag with cytokines is prepared by the addition of the reconstituted cytokine stocks to the medium. The recommended biological activities per mL medium are listed for each cytokine in Table 6.1.

- Before connecting the medium bag to the tubing set by sterile welding, collect medium from the medium bag with cytokines for the preparation of the transduction reagent bag or the gene modification reagent bag (see section 6.4 ´Preparation of transduction reagent´, 8.4.6 ´Transduction´ and 8.4.7 ´Gene modification´). Store at +2 to +8 °C (+36 to +46 °F) until preparation.

Cytokine	Recommended biological activity per mL final culture volume ($activity_{chamber}$)
SCF	300 *U*/mL
Flt3-Ligand	270 *U*/mL
TPO	1600 *U*/mL

Table 6.1: Overview of cytokines with recommended biological activities per mL medium

6.4 Preparation of transduction reagent

Prepare the transduction reagent under sterile conditions in a bag which should be connected to the tubing set by sterile welding. The volume of the transduction reagent bag is flexible in the range of 5 to 564 mL. It is recommended to use concentrated viral vector diluted in a volume of 10 mL.

- Transfer sufficient medium with cytokines into a container to end up in 10 mL total volume including the viral vector.
- Add concentrated viral vector into the container according to your requirements.
- Connect the transduction reagent bag to the tube on valve 5 (see section 8.4.6 ´Transduction´).

IMPORTANT
It is important to have a backup vial of viral vector available. This backup is for the case that a user error happens during the manual preparation of the vector.

7

Process configuration and preparation

The following section describes the configuration and preparation of the CliniMACS Prodigy HSCT-LS System. This includes the initialization of the instrument by selecting the HSCT-LS process. After parameter input, the tubing set is installed stepwise. Subsequently, the medium bag without cytokines is connected and the tubing set is filled with medium (tubing set priming).

7.1 Initialization of the CliniMACS Prodigy

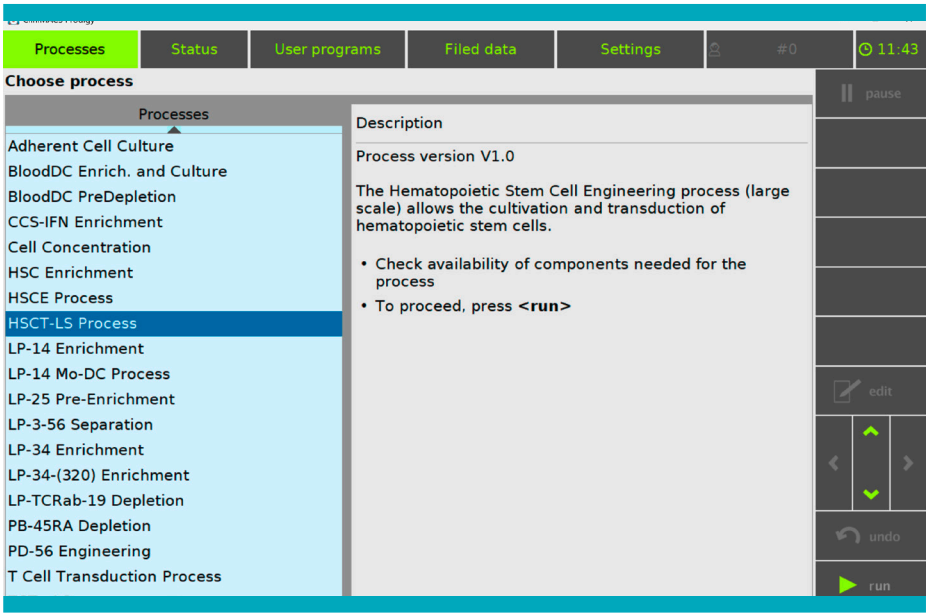
For initialization of the CliniMACS Prodigy, switch on the instrument with the power switch located on the rear side of the instrument.

IMPORTANT
A user interface showing screens with instructions and pictures will guide through the entire procedure. 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 tool bar to operate the instrument. For details, refer to the CliniMACS Prodigy Instrument user manual.

⚠ CAUTION

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

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



Screen 7.1: Main screen – Choice of HSCT-LS process

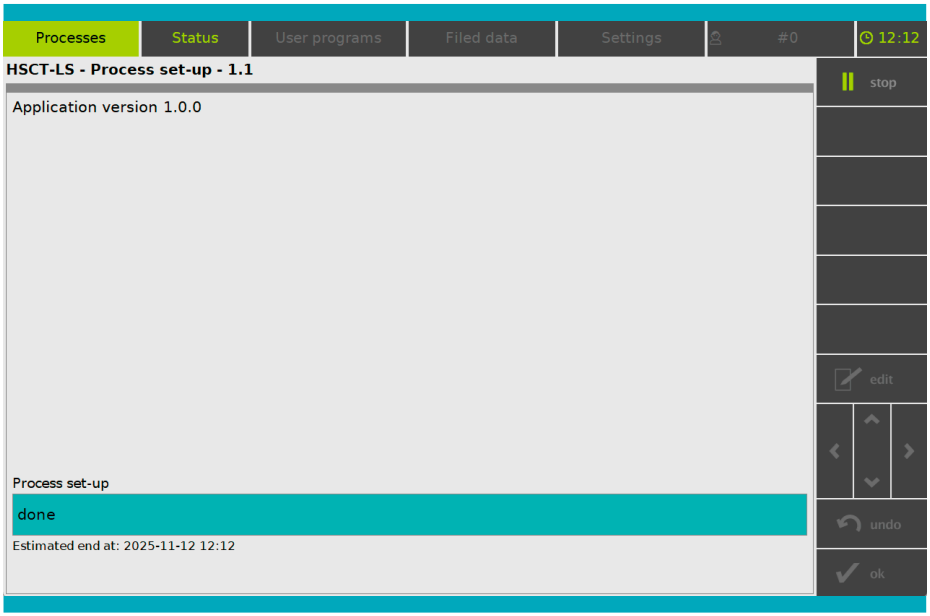
After the instrument initialization phase, the main screen is shown. Select the "HSCT-LS Process" and tap < run > to confirm the selection (see Screen 7.1).

⚠ CAUTION

Risk of process failure. If the incorrect drive shaft is installed on the instrument, the HSCT-LS process is not executed. The HSCT-LS System is designed for the use with the CliniMACS Prodigy TS 620 only. The CliniMACS Prodigy TS 620 contains a large CentriCult™ Chamber requiring a specific drive shaft.

- Ensure the drive shaft is installed by Miltenyi Biotec Instrument Service before using the tubing set. Any CliniMACS Prodigy with serial number (SN) 490 or lower needs the installation of the new drive shaft. Instruments with SN higher than 490 are already equipped with the new drive shaft.

Contact Miltenyi Biotec Technical Support, in case a drive shaft exchange is required. 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.

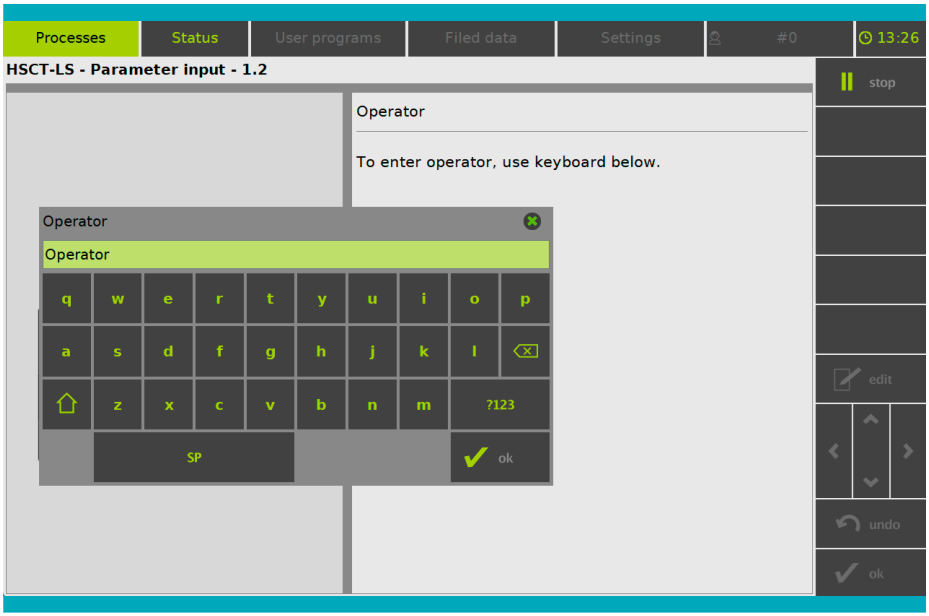


Screen 7.2: HSCT-LS process set-up

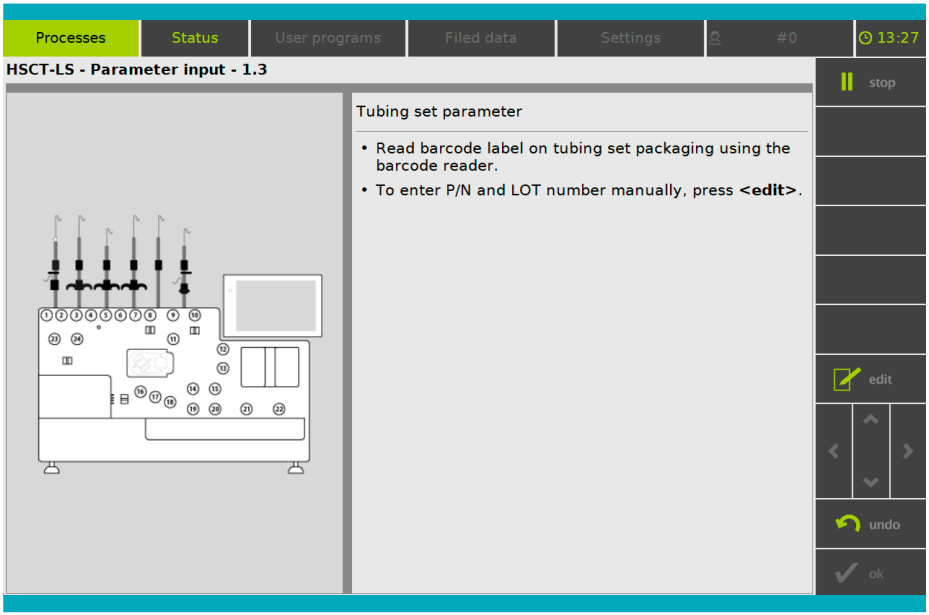
7.2 Parameter input and process setup

Multiple parameters can be entered for the HSCT-LS System using either the barcode reader attached to the instrument or the keyboard shown on the screen. Tap <ok> to confirm. All entered parameters are saved in a process-related protocol.

Within the next steps of the process enter information related to the user (see Screen 7.3) and CliniMACS Prodigy TS 620 (see Screen 7.4). For the manual entry of capital letters, tap <⇧>, for space tap <SP>, for numbers tap <?123>, and for backspace tap <⌫>.

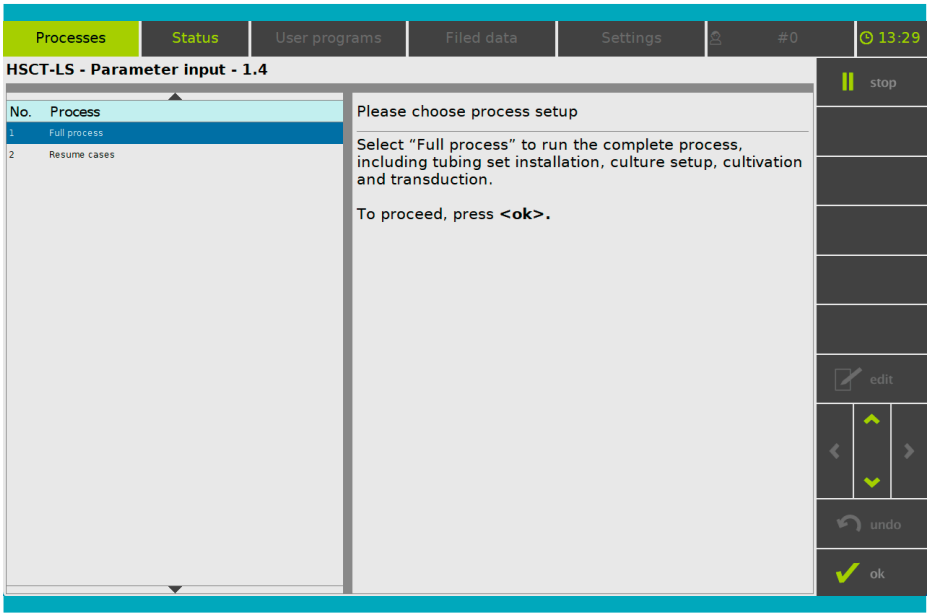


Screen 7.3: Entry of operator-related information



Screen 7.4: Entry of CliniMACS Prodigy TS 620 part number (P/N) and lot number (LOT)

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



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

After the input of user-related and tubing set-related information, choose between two different options:

1 Full process or

2 Resume cases (see section 4.2 ´Process overview´).

"1 Full process" is chosen to run the full process starting from tubing set installation until end of culture (see Screen 7.5).

7.2.1 Resume cases

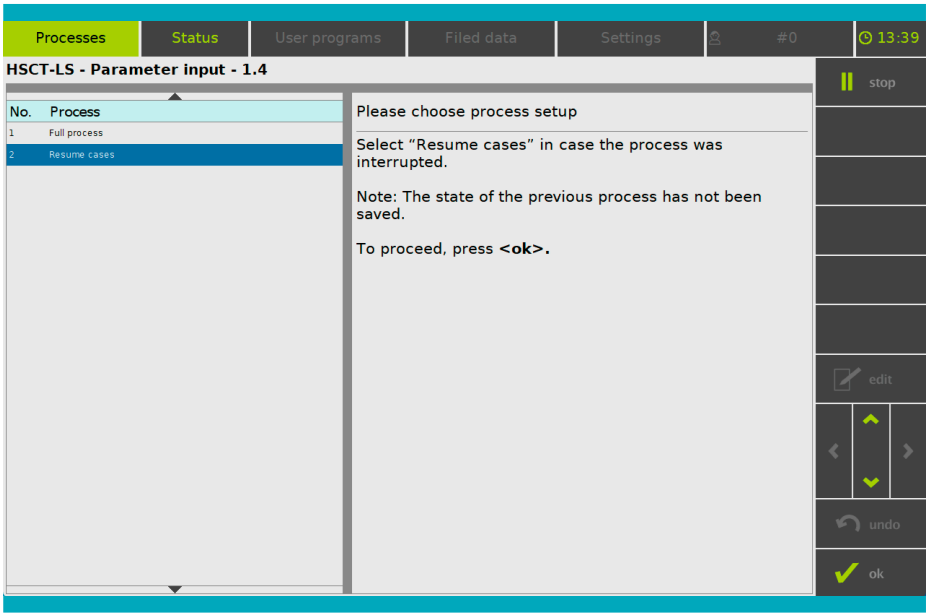
In case the cultivation process was interrupted or harvest of the cells needs to be resumed, it is possible to select "2 Resume cases" after restarting the instrument (see Screen 7.6).

Choose between two different cases:
"2.1 Resume HSC cultivation" or "2.2 Resume end of culture" (see Screen 7.7).

⚠ CAUTION

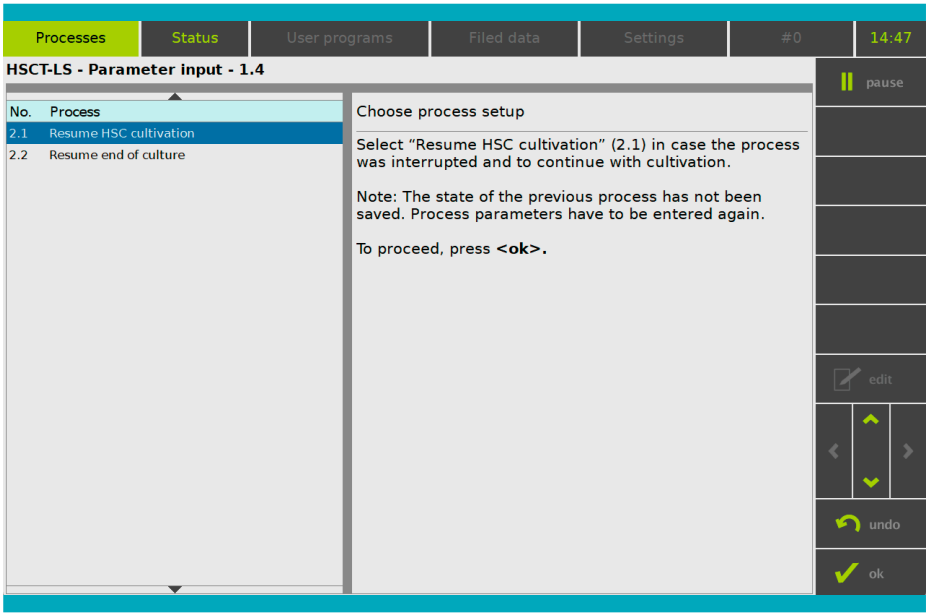
Risk of low performance or loss of the cell product. If the process is interrupted there is the risk of low performance or loss of the cell product.

- Choose "Resume cases" to continue the cell cultivation process or to start the end of culture.



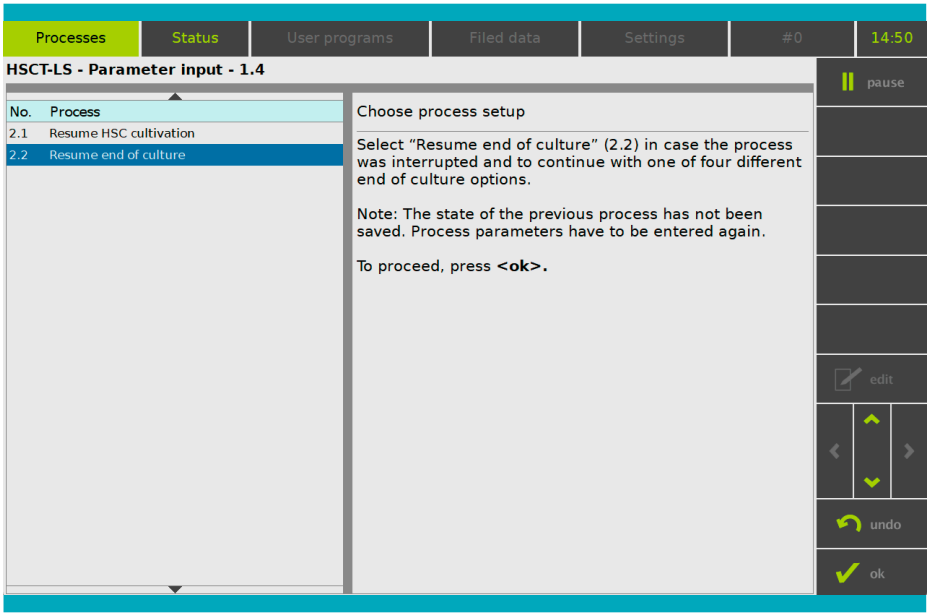
Screen 7.6: Resume cases

"2.1 Resume HSC cultivation" starts directly with the setup of the HSCT-LS protocol for the cultivation of the cells. The activity matrix must be set up and the CO_2 concentrations as well as the current volume must be entered (see Screen 7.7).



Screen 7.7: Resume HSC cultivation

"2.2 Resume end of culture" starts directly with the selection of one of the four end of culture types without further cultivation of the cells (see Screen 7.8).



Screen 7.8: Resume end of culture

Both resume cases do not include the tubing set installation, the tubing set priming and the transfer of the cells into the chamber. The current culture volume in the chamber must be entered manually.

IMPORTANT

Be aware that entries in the activity matrix and logfile protocol entries are not saved on the instrument after an unexpected shutdown. When case 2.1 is executed the user must start with a new activity matrix and the current day refers to day 0.

This user manual describes the complete process using case 1 (Full process) as the default process (see Screen 7.5).

7.3 Tubing set installation

This section outlines the components of the CliniMACS Prodigy TS 620, the preparation of the tubing set, and its stepwise installation, which is the first step in the option "Full process" (see Figure 7.1).

7.3.1 Components of the CliniMACS Prodigy TS 620

The components of the CliniMACS Prodigy TS 620 are pre-assembled and provided in a sealed and sterilized package. All components of the tubing set are summarized in Figure 7.1.

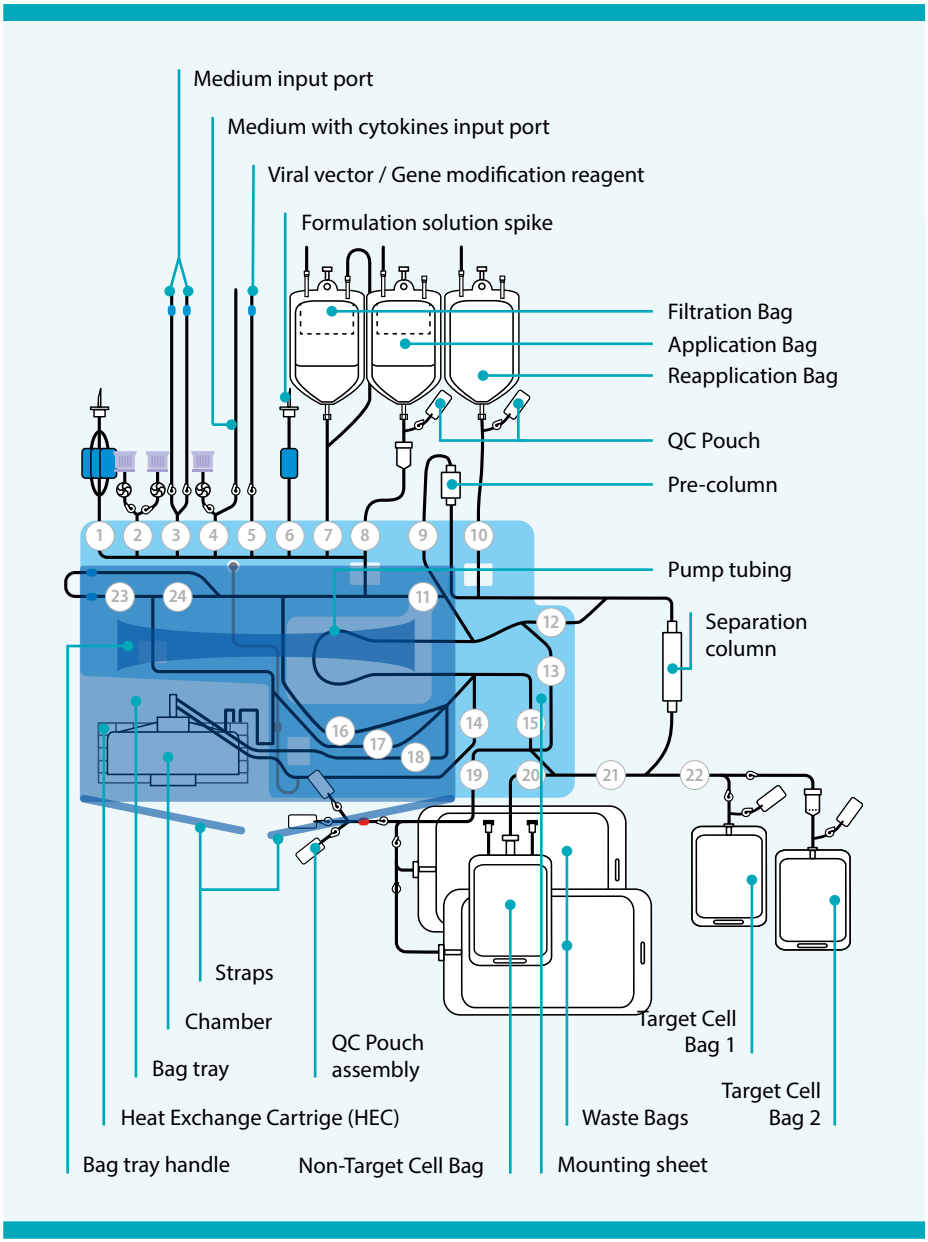


Figure 7.1: Components of the CliniMACS Prodigy TS 620

7.3.2 Installation steps

This section outlines the preparation of the tubing set, its stepwise installation and the integrity test to test the tubing set for leaks.

⚠ WARNING

Risk of contamination. If packaging is damaged, the tubing set may no longer be sterile and therefore should not be used.

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

⚠ WARNING

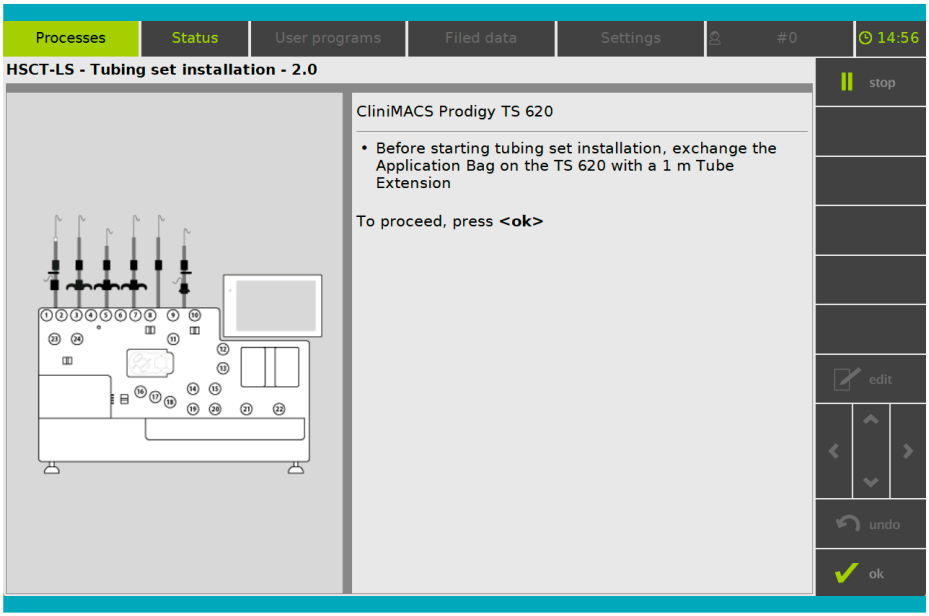
Risk of contamination. In case of unsterile working conditions, there is the risk of contamination of the target cells.

- Use aseptic working conditions for the preparation of the tubing set and its stepwise installation.

Preparation of the tubing set

Before installation, preparation of the tubing set TS 620 is required to enable safe connection of the cellular starting material (cell bag) in the later procedure:

- Replace the Application Bag with a 1 m Tube Extension by sterile welding to provide enough tubing for a safe connection of the cell bag after the installation of the tubing set (see Screen 7.9 and Figure 7.2). A transfer of the cellular starting material into the Application Bag is not recommended as it may result in cell loss due to the general transfer procedure.
- Ensure that the drip chamber and the QC Pouch are still part of the tubing set after sterile welding.



Screen 7.9: Exchange of Application Bag with 1 m Tube Extension by sterile welding

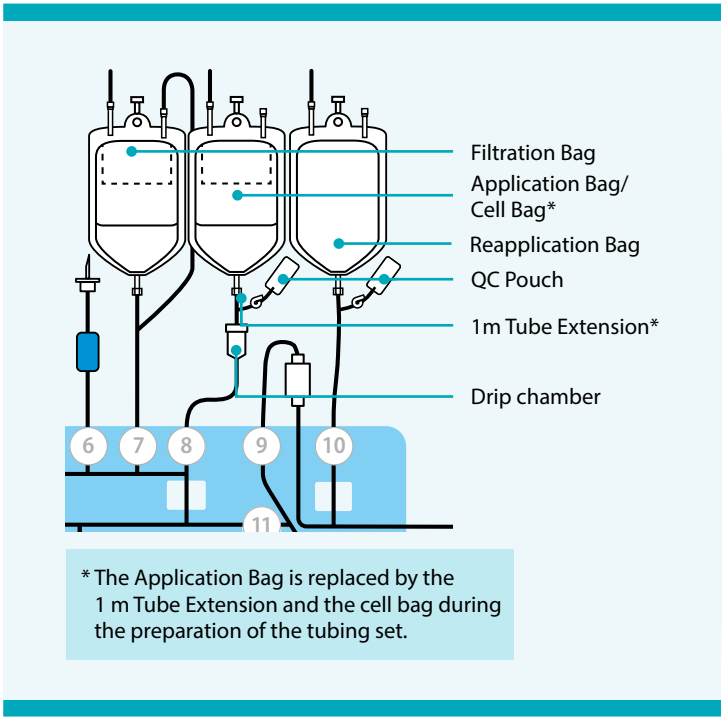
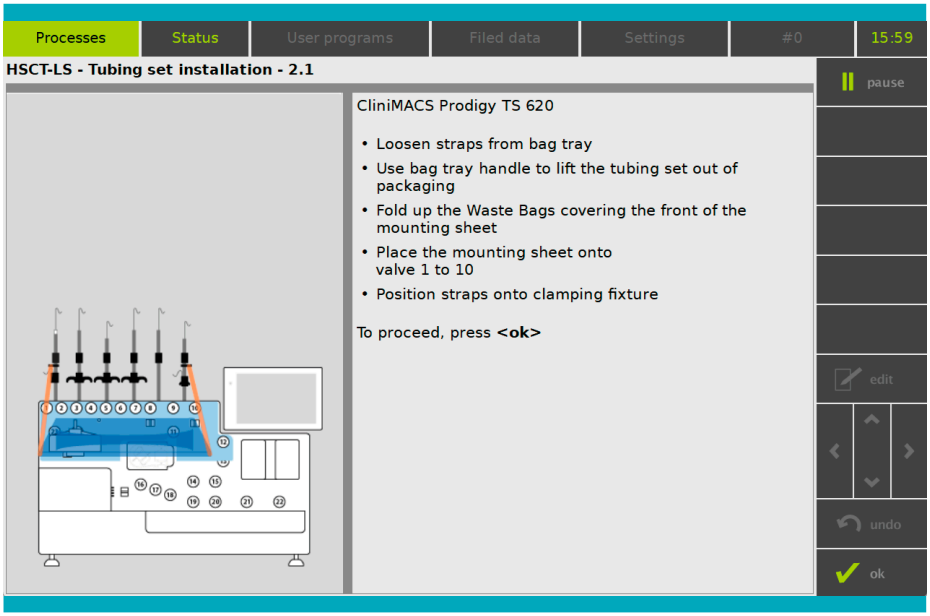


Figure 7.2: Components for the preparation of the tubing set (detailed)

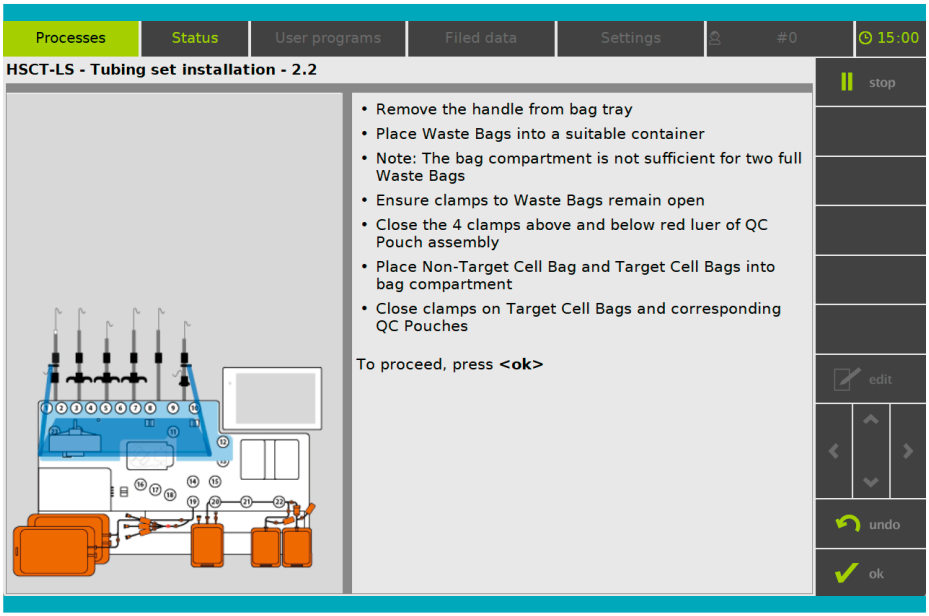
Stepwise installation of the tubing set

This section guides the user step by step through the installation of all tubing set components (see Screen 7.10 to Screen 7.30) and the integrity test to check the tubing set for potential leaks (see Screen 7.31 to Screen 7.32).

Each screen shows the written instructions supported by an informative image. Blinking and orange features in an image indicate areas of attention. At any step during the installation tap <undo> to return to a previous step.



Screen 7.10: Installation of bag tray and mounting sheet onto the instrument



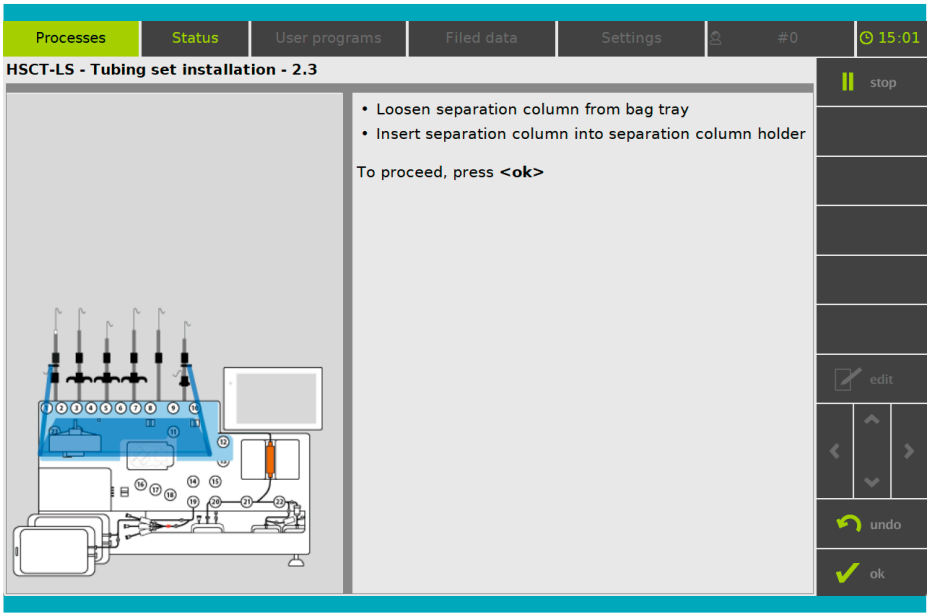
Screen 7.11: Placement of bags into bag compartment and closure of clamps

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

The CliniMACS Prodigy TS 620 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.

IMPORTANT
Ensure that the clamps on the QC Pouches attached to Target Cell Bags are closed.



Screen 7.12: Insertion of separation column into magnet unit

Figure 7.3 shows how to insert the separation column into the column holder of the magnet unit.

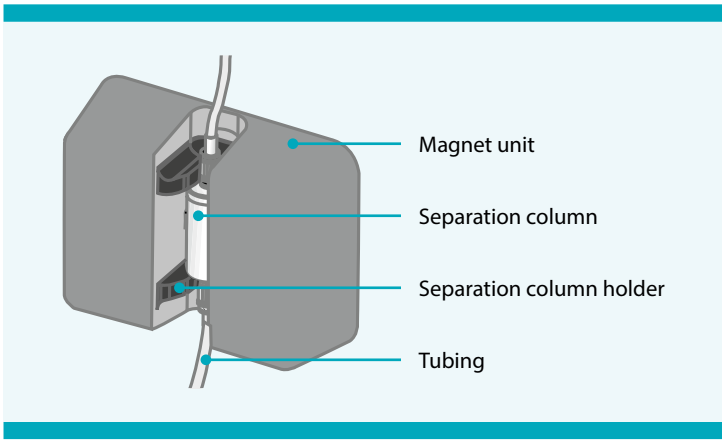


Figure 7.3: Separation column inserted into magnet unit

⚠ WARNING

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

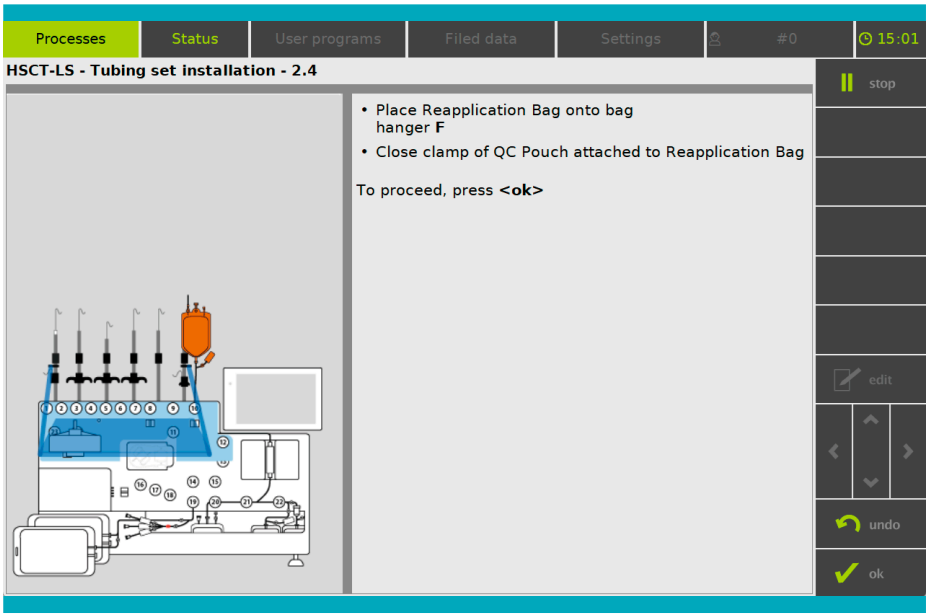
- Only insert or remove the separation column when the magnet unit is switched off.

⚠ CAUTION

Risk of pinch injury. If the column is not inserted correctly, there is the risk of pinch injury.

- Hold the top and bottom part of the column between thumb and index finger. The column label should be facing towards the user.

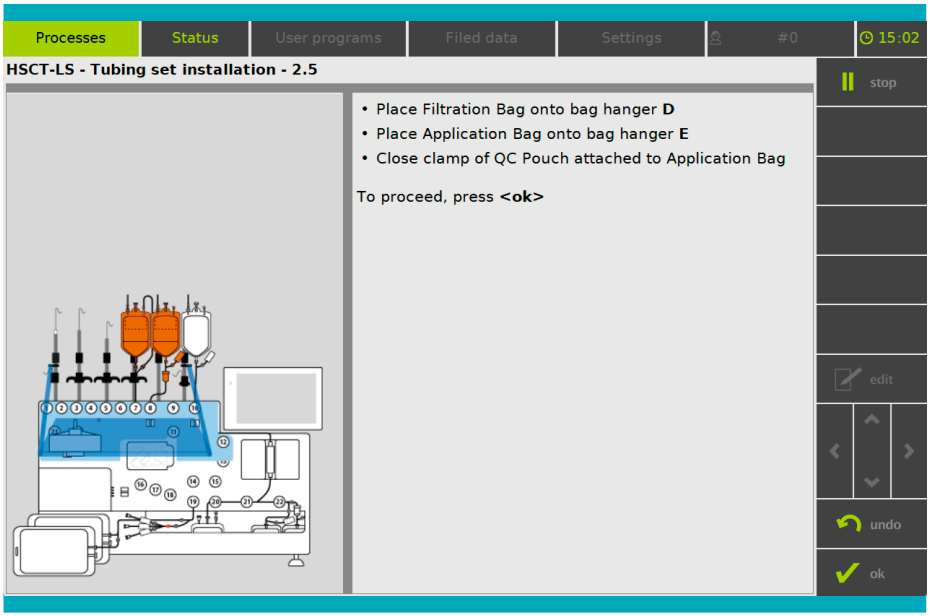
- Place the column carefully into the column holder. Ensure that no tubing is pinched between column and column holder.



Screen 7.13: Installation of Reapplication Bag

IMPORTANT

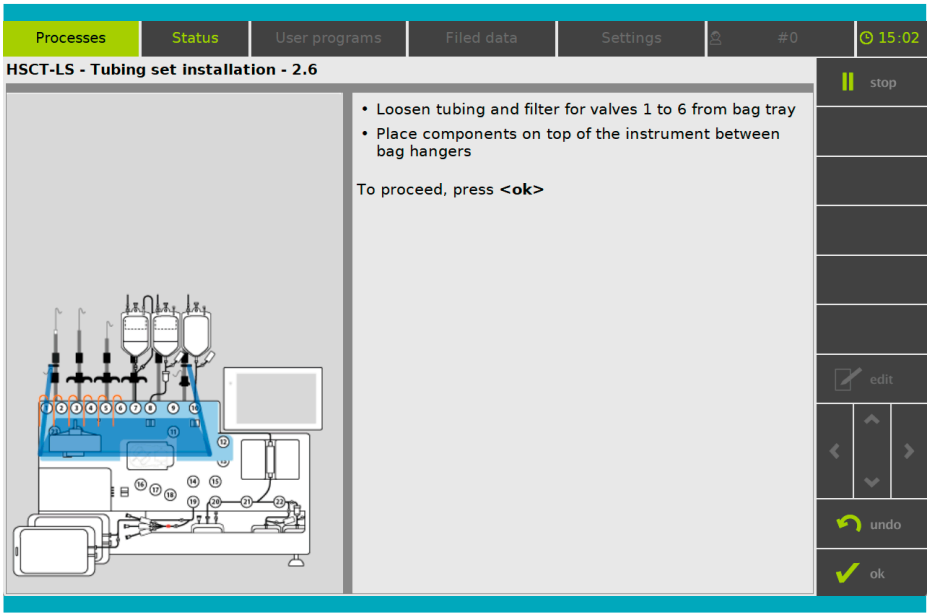
Ensure that the clamp on the QC Pouch attached to the Reapplication Bag is closed.



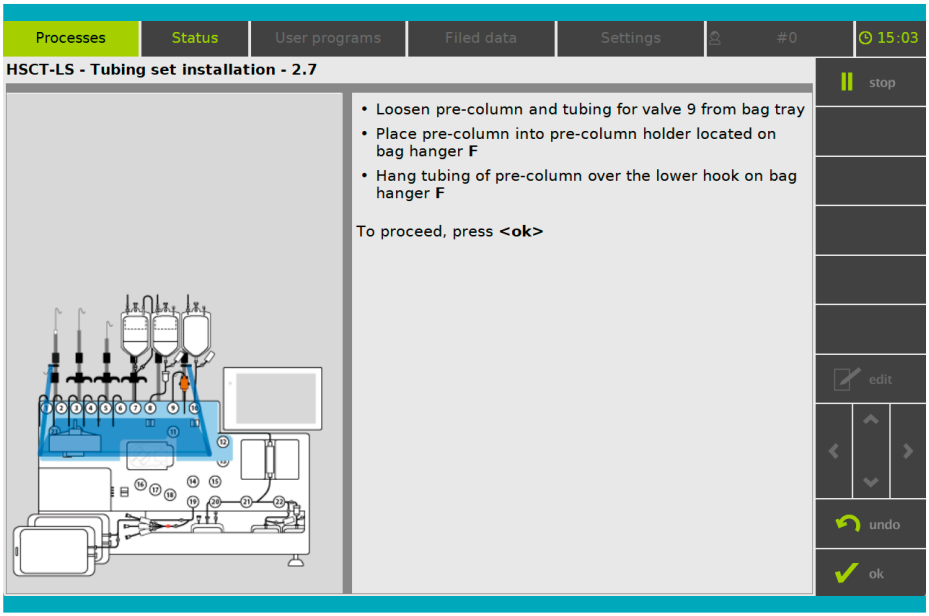
Screen 7.14: Installation of Filtration Bag and 1 m Tube Extension (still termed Application Bag here)

IMPORTANT

Ensure that the clamps on the QC Pouches attached to the 1 m Tube Extension are 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 7.4 shows how to place the tubing over the lower hook on bag hanger (F).

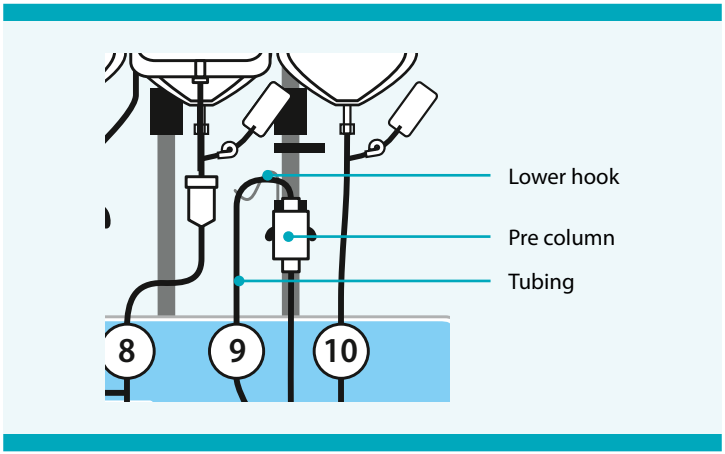
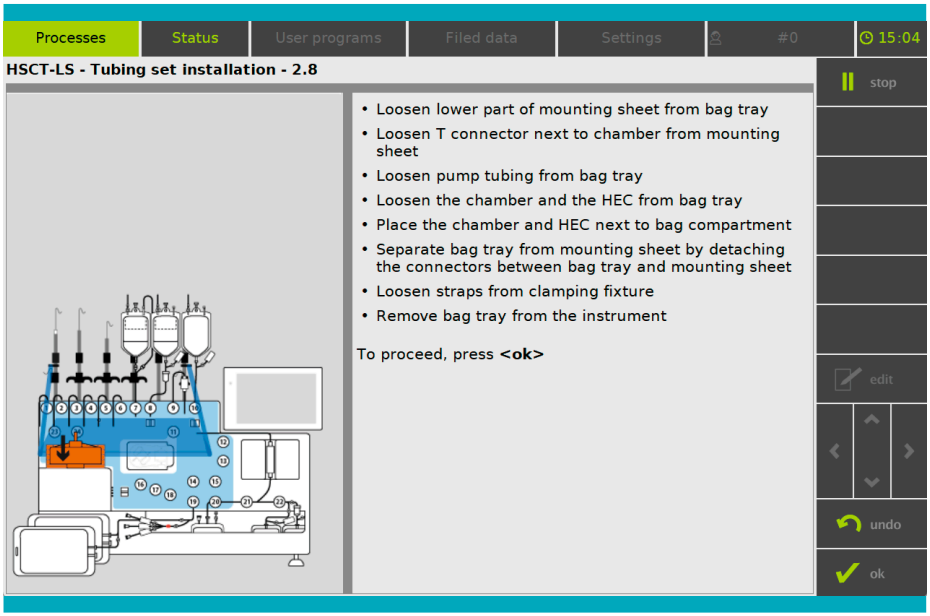
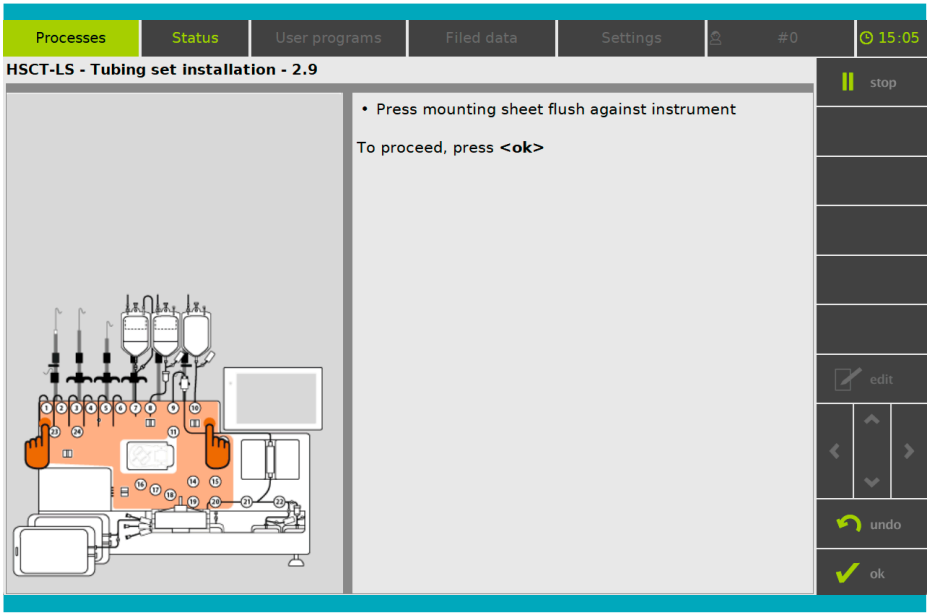


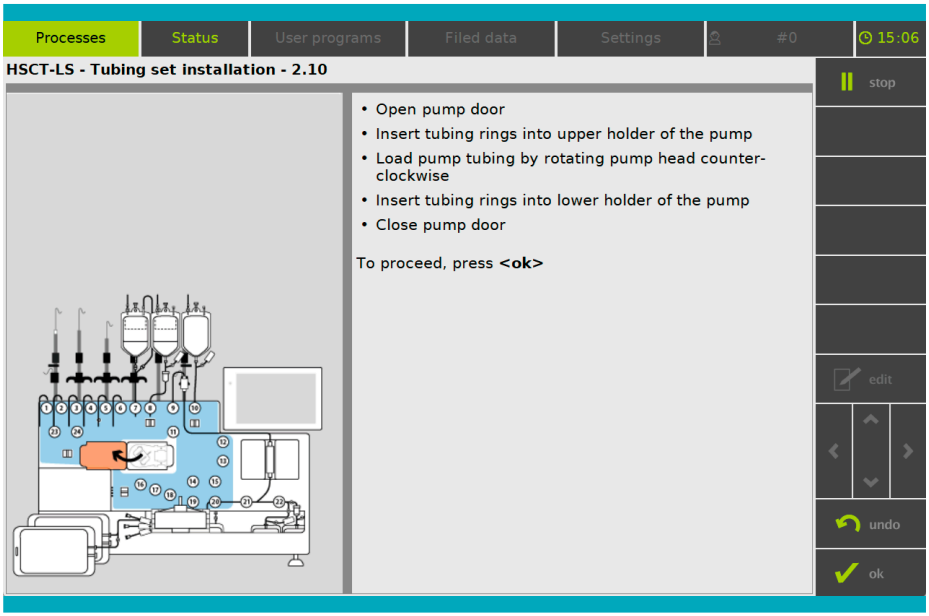
Figure 7.4: Guidance of pre-column-associated tubing



Screen 7.17: Removal of bag tray from instrument



Screen 7.18: Press mounting sheet flush against the instrument



Screen 7.19: Insertion of pump tubing into pump

Figure 7.5 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.
3. 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.

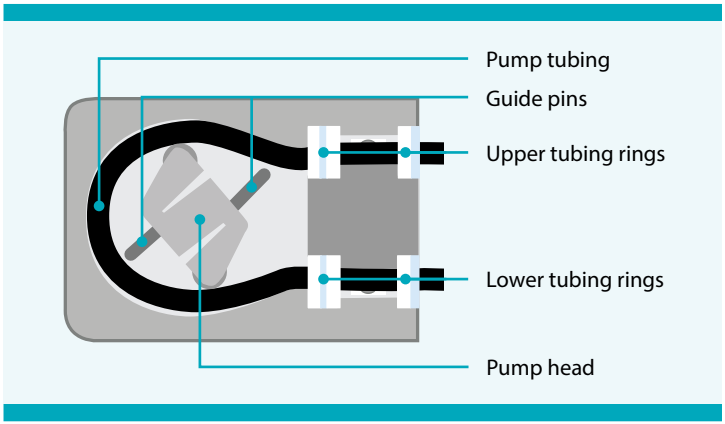
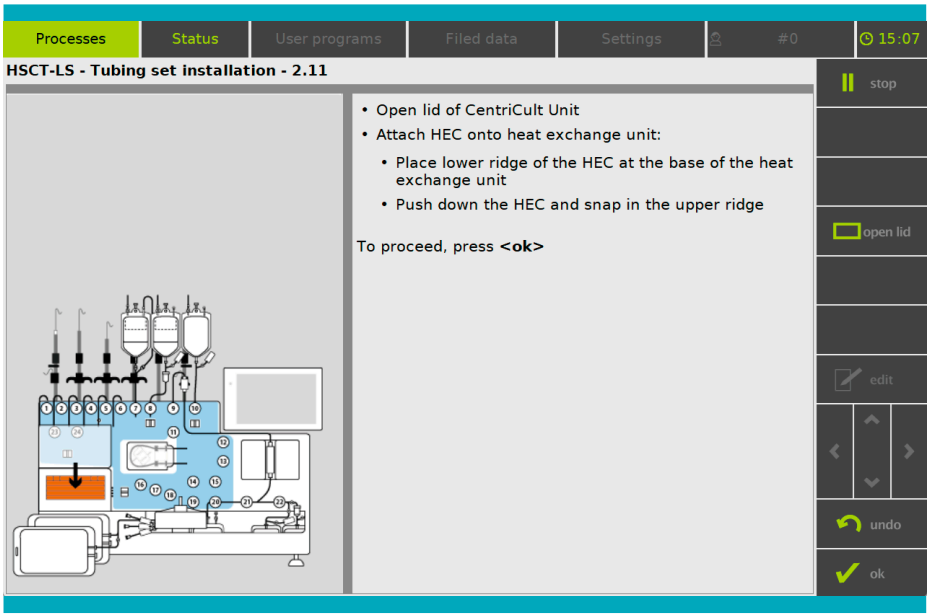


Figure 7.5: Pump tubing inserted into pump

The CentriCult Unit lid will unlock automatically for the installation of the Heat Exchange Cartridge (HEC) and chamber (see Screen 7.20). 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 7.6 to Figure 7.8 illustrate 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.

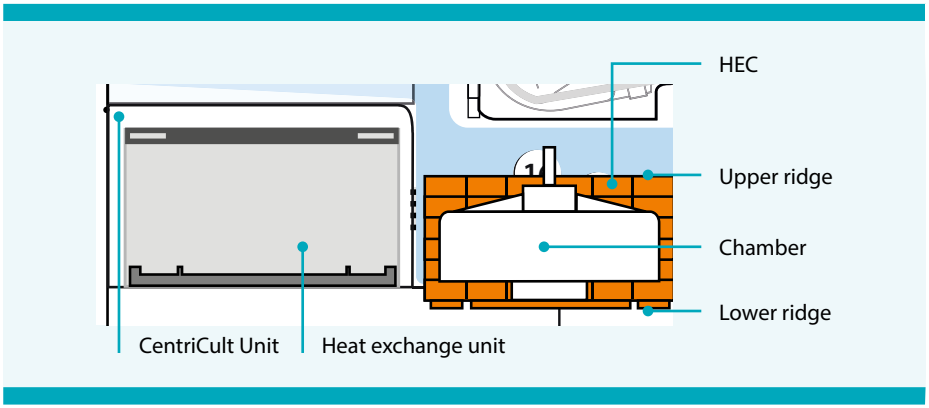


Figure 7.6: Step 1 – Loosen the HEC from chamber

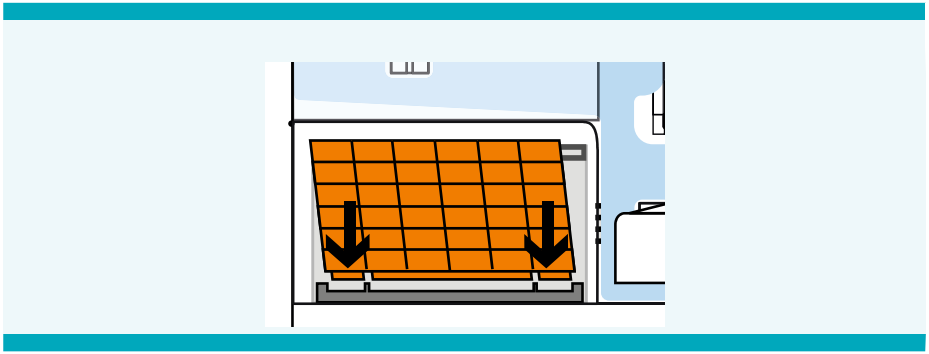


Figure 7.7: Step 2 – Place lower ridge of the HEC at the base of heat exchange unit

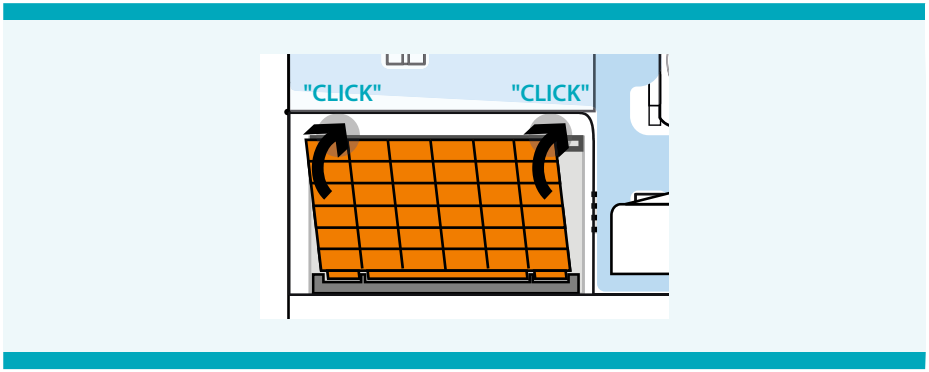
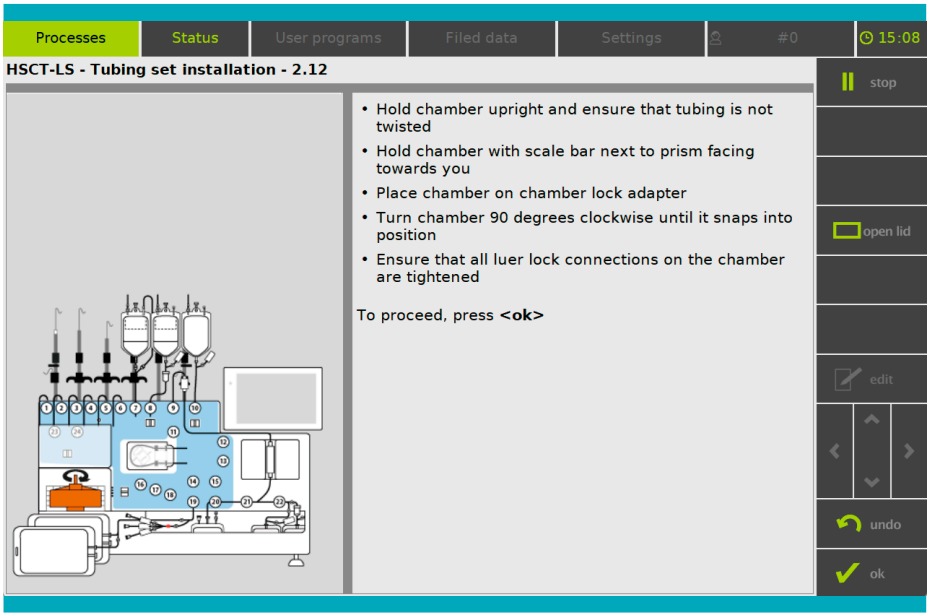


Figure 7.8: Step 3 – Push down the HEC and snap in upper ridge

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



Screen 7.21: Installation of chamber into CentriCult Unit

Figure 7.9 shows the components of the CentriCult Unit.

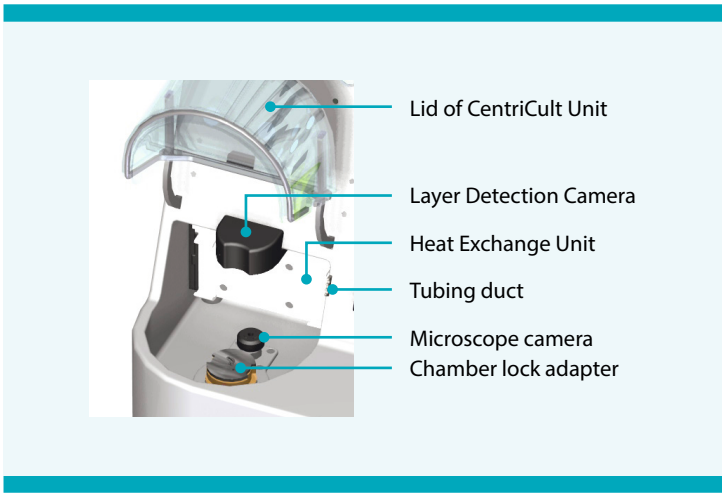


Figure 7.9: Components of the CentriCult Unit

IMPORTANT

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

NOTICE

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

- Before positioning the chamber onto the chamber lock adapter, 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.

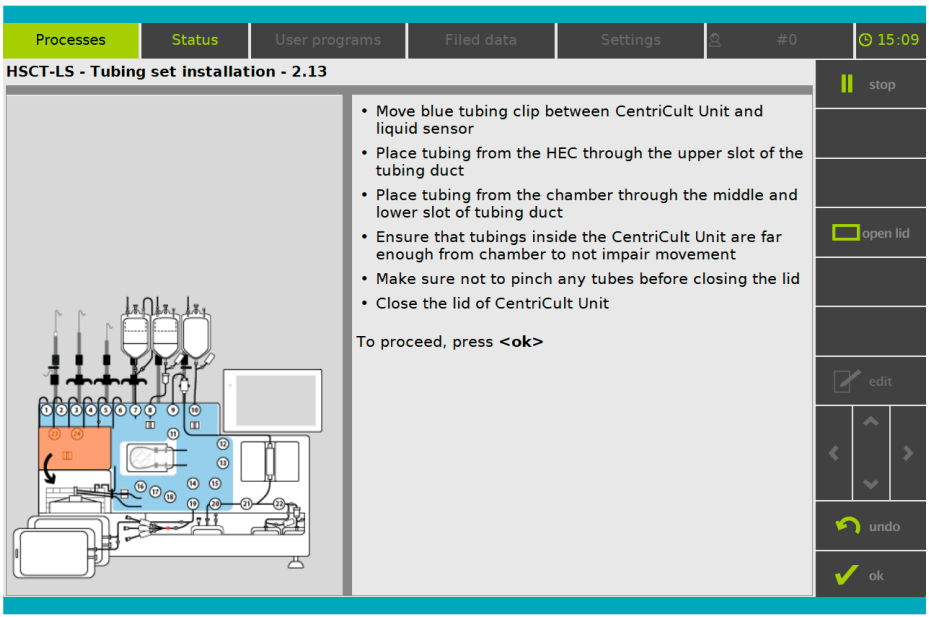
⚠ CAUTION

Risk of process failure. An incorrectly installed chamber can cause a process failure.

- Ensure that the chamber is tightly locked in position.
- Ensure that the chamber does not touch tubes leading to the HEC to prevent tube destruction during chamber rotation.
- Do not use the tubing set if the chamber cannot be installed properly.

Refer to important drive shaft requirements specified in section 7.1 ´Initialization of the CliniMACS Prodigy´.

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 for tubings from HEC and chamber through slots of tubing ducts

Figure 7.10 illustrates how to insert the two chamber tubing lines through the tubing duct. Ensure that the tubing is not twisted or pinched by the lid of the CentriCult Unit.

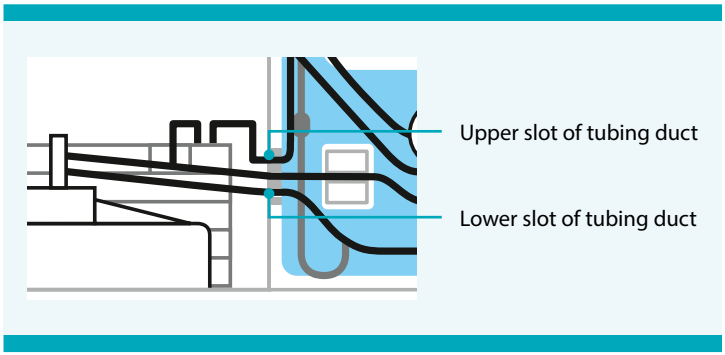
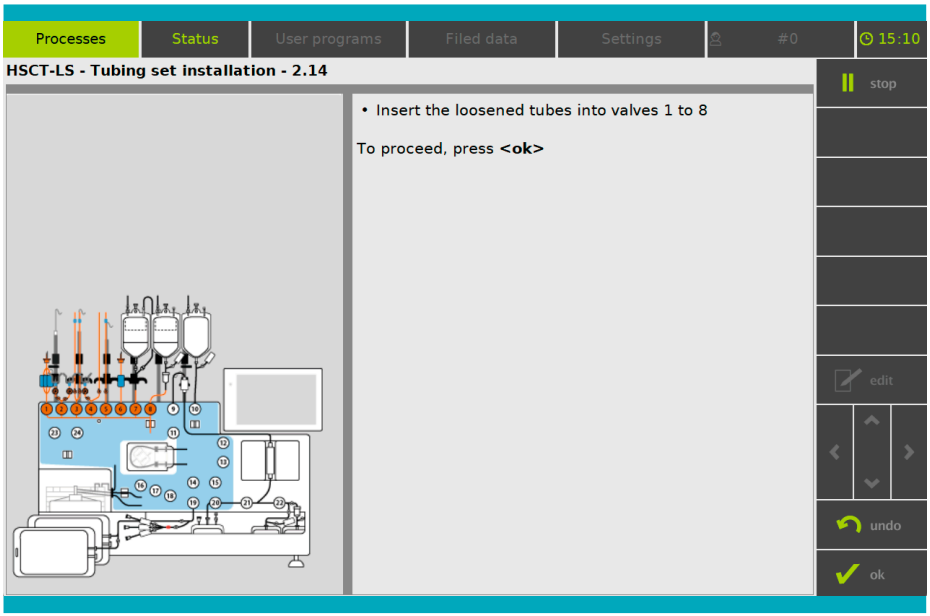


Figure 7.10: Guidance of tubing through tubing duct



Screen 7.23: Insertion of tubing into valves 1 to 8

Figure 7.11 shows how the tubing is 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 must be adjusted, press the valve button to open the valve before adjustment.

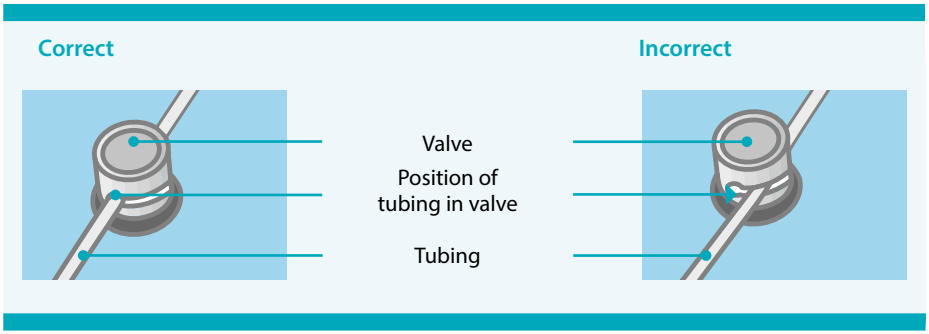
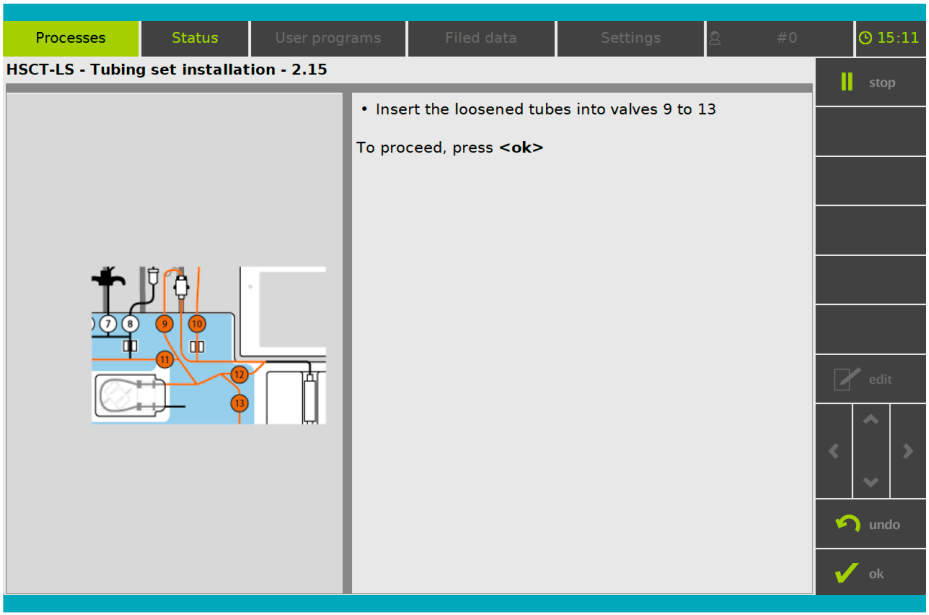


Figure 7.11: Insertion of tubing into valves



Screen 7.24: Insertion of tubing into valves 9 to 13

Figure 7.12 shows how to insert the tubing correctly into valve 10, 12 and 13.

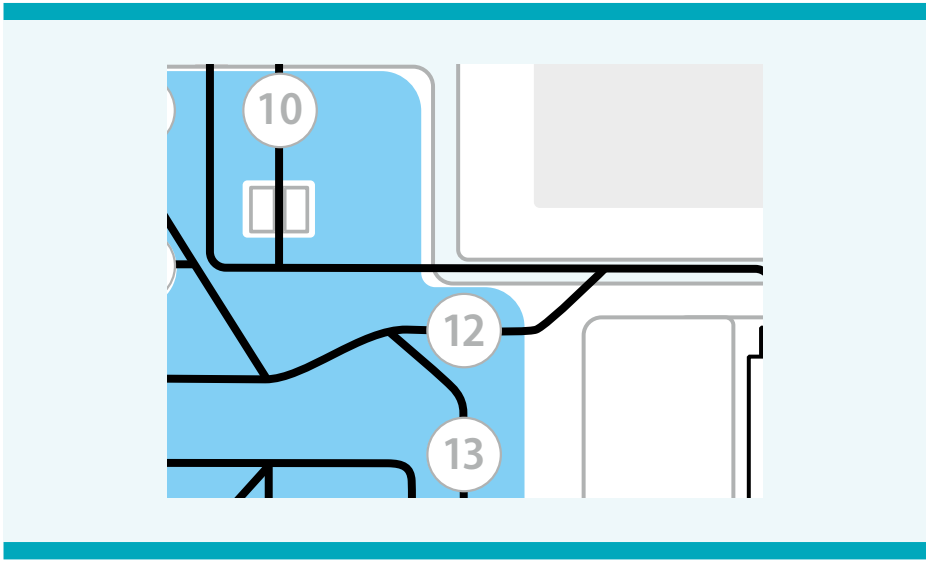
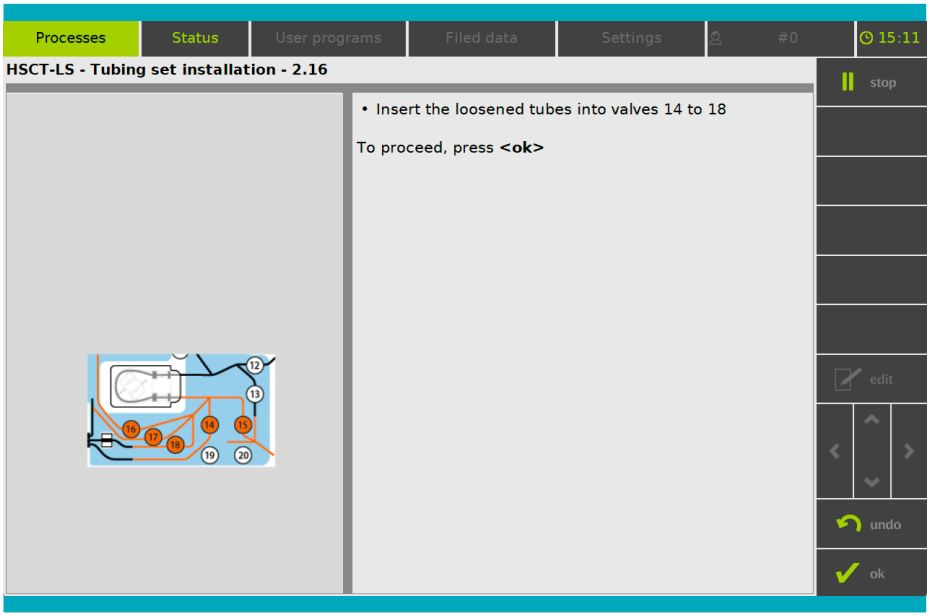
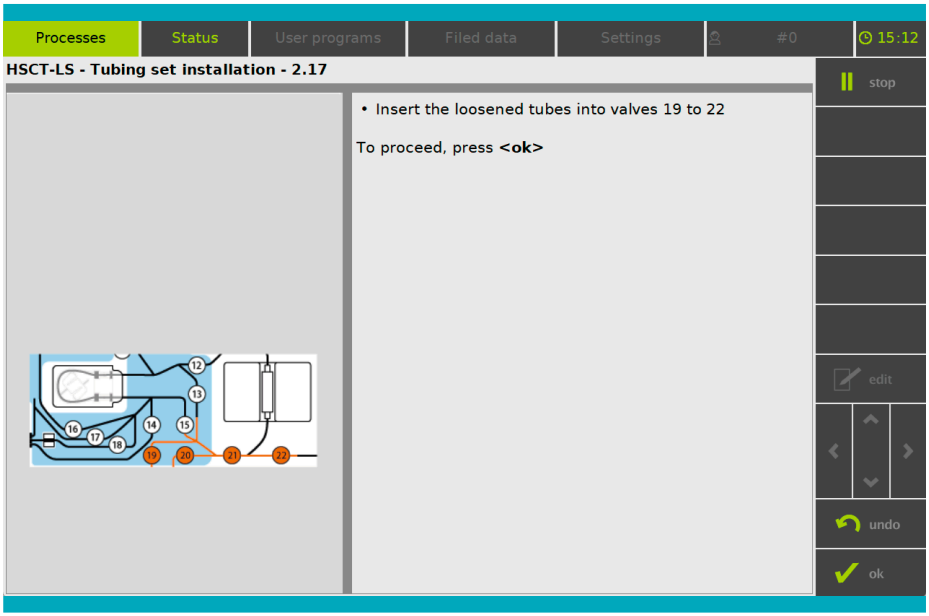


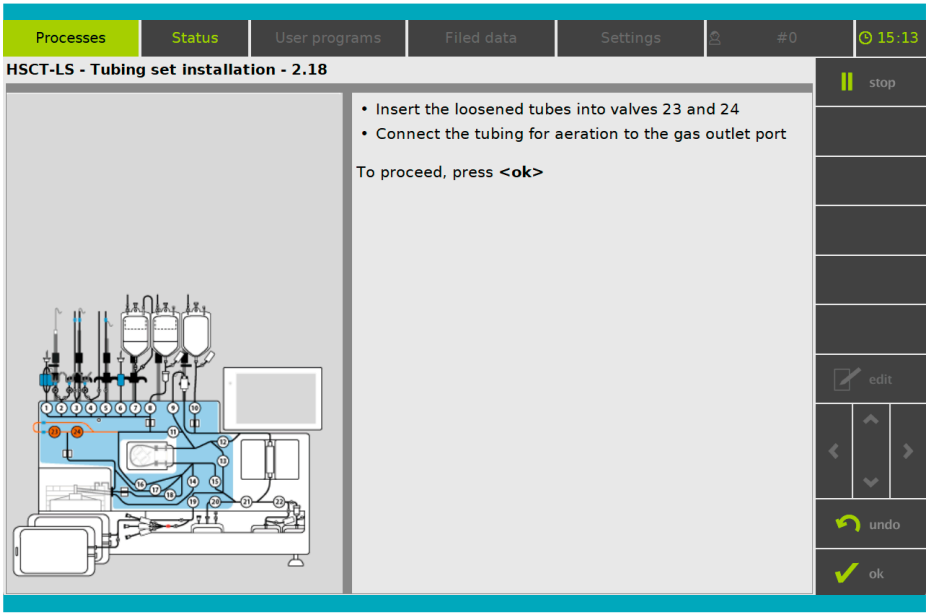
Figure 7.12: Guidance of tubing for separation column and valves 10, 12 and 13



Screen 7.25: Insertion of tubing into valves 14 to 18



Screen 7.26: Insertion of tubing into valves 19 to 22

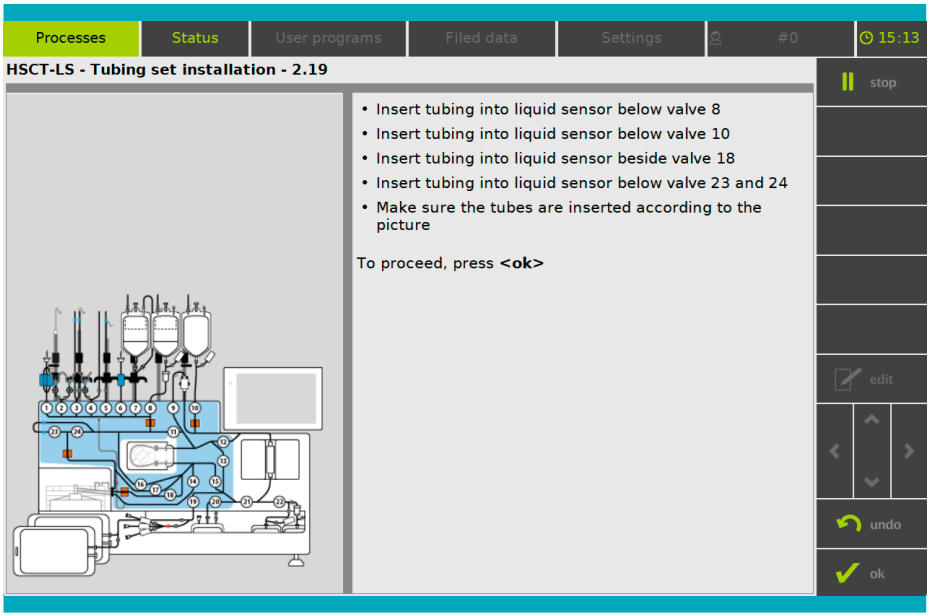


Screen 7.27: Insertion of tubing into valves 23 to 24 and connection of tubing for aeration to the gas outlet port

⚠ WARNING

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

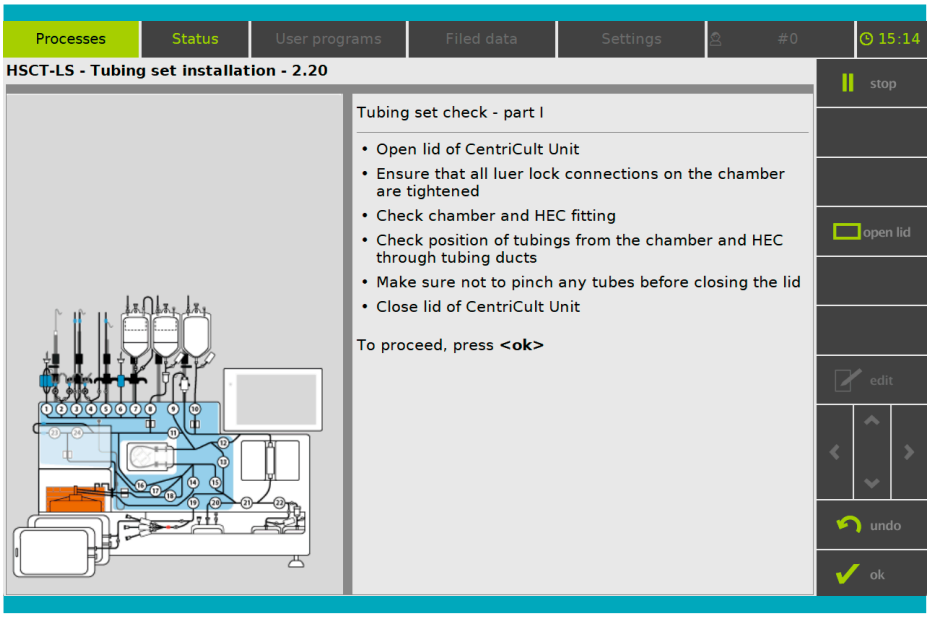
- Tightly connect the tubing for aeration to the gas outlet port to ensure a proper gas flow into the cultivation chamber.



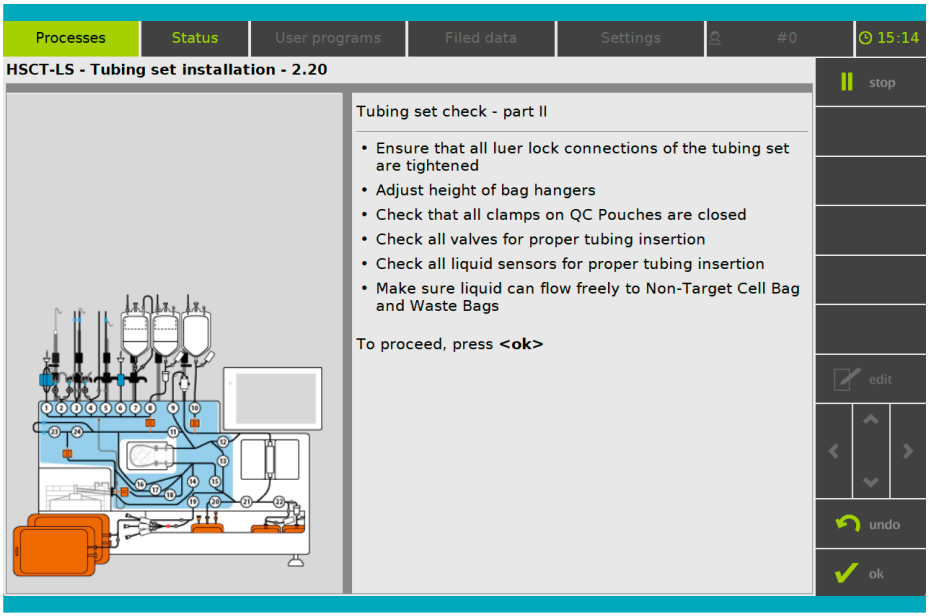
Screen 7.28: Insertion of tubing into liquid sensors

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 7.29: Tubing set check – part I



Screen 7.30: 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 (see Figure 7.11). If a tubing position must be adjusted, press the valve button to open the respective valve beforehand.

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 prevent 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, tap <open lid> on the tool bar.

Furthermore, it is possible to remove and re-insert the chamber at this step, (for example if the chamber tubing has been twisted during installation). In case the chamber needs to be removed, tap <open lid> on the tool bar. 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.

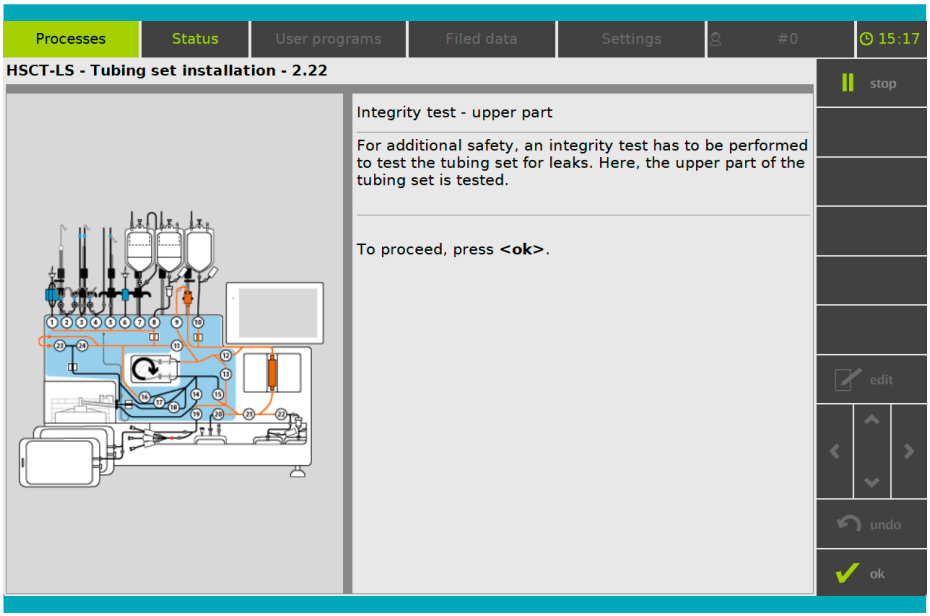
When the tubing set installation is complete, all valves will open and close twice to verify proper

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.

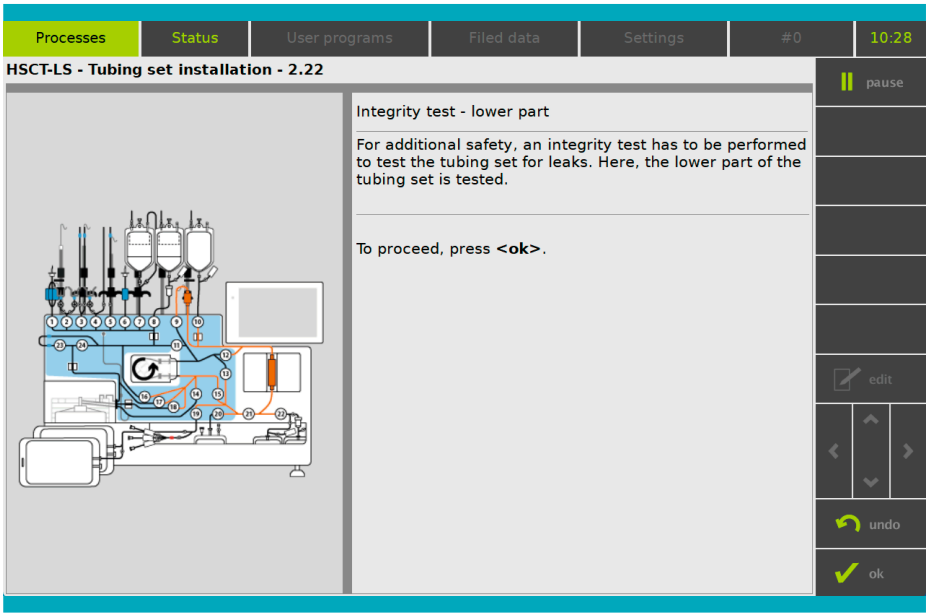
IMPORTANT

For additional safety, an integrity test must be performed to test the tubing set for leaks.

The test consists of two automated sequences that apply controlled overpressure separately to the upper and lower part of the tubing set. Follow the instructions on the screen to start the integrity test for the upper and lower part of the CliniMACS Prodigy TS 620. It is not recommended to tap <no> and skip the integrity test in the following pop-up. Perform separate integrity tests for both upper and lower part of the tubing set.



Screen 7.31: Integrity test for upper part



Screen 7.32: Integrity test for lower part

⚠ WARNING

Risk of cell loss or 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 the upper and lower integrity test.
- Contact Miltenyi Biotec Technical Support for assistance, if required.

7.4 Tubing set priming

This section outlines the connection of medium to the tubing set followed by priming of the tubing set.

7.4.1 Connection of medium

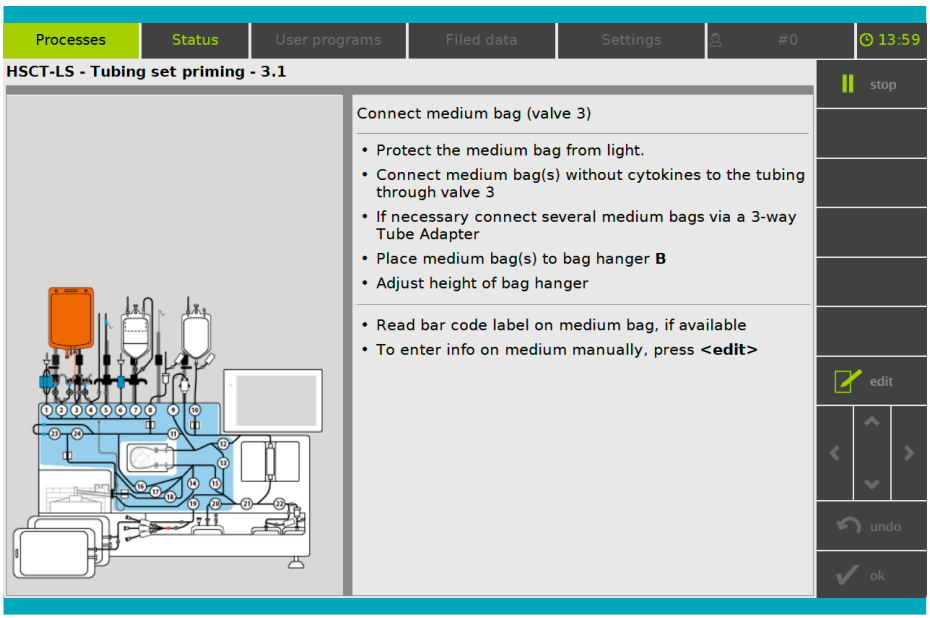
Refer to chapter 6 ´Preparative steps´ for the preparation of the medium. If medium is provided in 500 mL bags, three bags must be connected via a 3-way Tube Adapter.

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 7.33 to Screen 7.36 will guide the user through the priming phase.



Screen 7.33: Connection of medium bag

IMPORTANT

Light could lead to adverse effects on the HSC Brew GMP Medium, therefore it should be protected from light.

To connect the medium bag or the free end of the 3-way Tube Adapter 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. Alternatively, tap <edit> to enter part number (P/N) and lot number (LOT) manually with the keyboard.

IMPORTANT
Confirm that the clamp of the medium bag is open at this point.

Tap <edit> to enter information on supplements and HSA. 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.

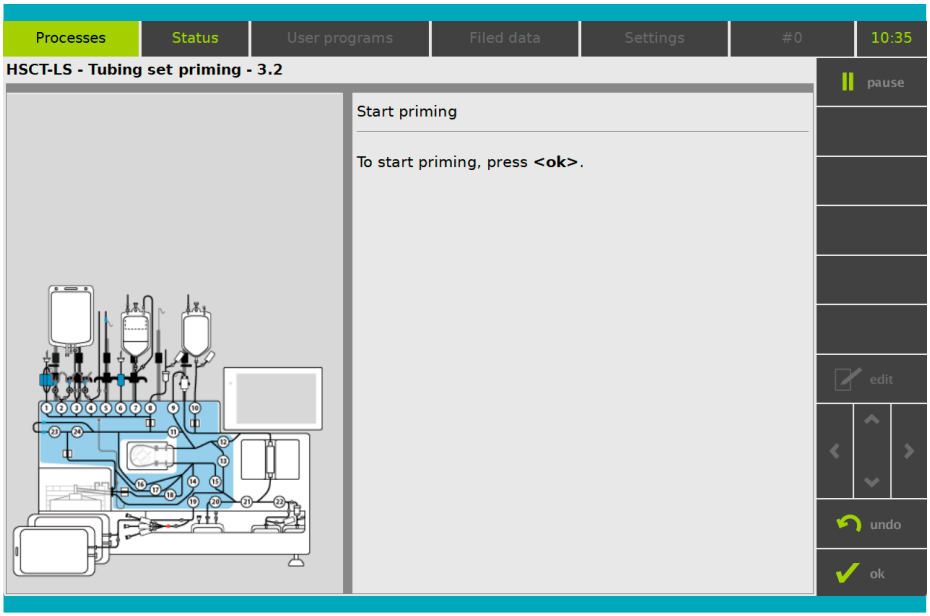
IMPORTANT
It is recommended to use HSC Brew GMP Medium for the HSCT-LS System. Using other medium could result in a lower performance.

Bag hanger ID	Bag	Input port
A		
B	Medium bag	3
C	Medium bag with cytokines	4
D	Filtration bag	7
E	Cell bag (Connected to TS620 via 1 m Tube Extension)	8
F	Reapplication bag	10

Table 7.1: Positions of bags on bag hangers during culture setup

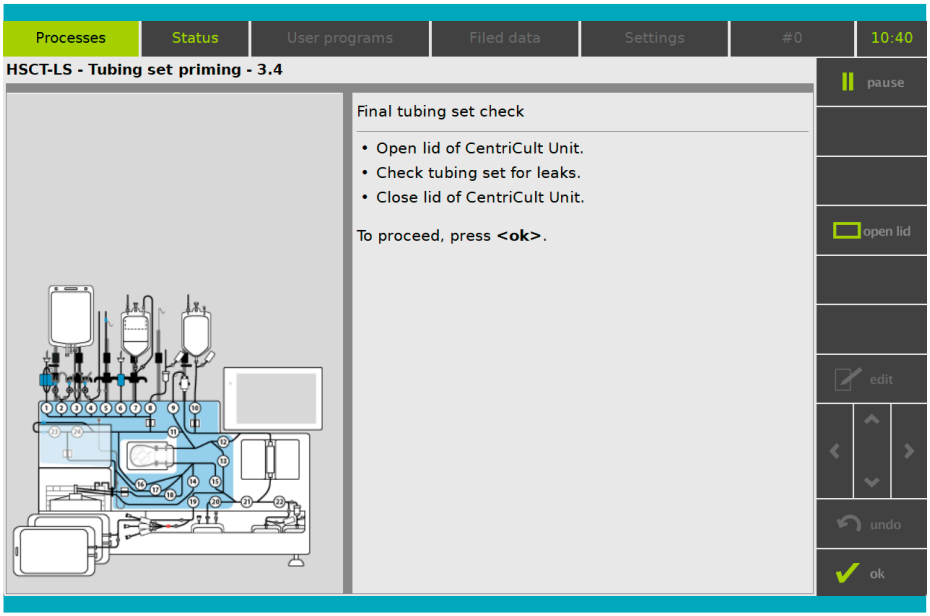
7.4.2 Priming phase

During the priming phase, the Reapplication Bag and the tubing set is filled with medium.



Screen 7.34: Start of priming phase

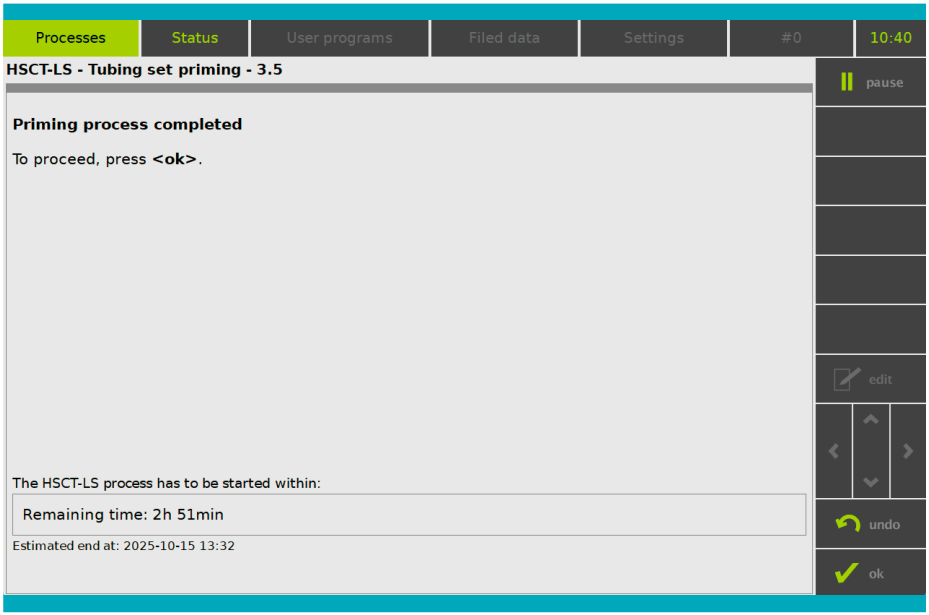
To start the priming of the tubing set tap <ok>. The remaining time for the priming phase will be shown as a process bar.



Screen 7.35: Final tubing set check after priming phase

When the priming phase is completed, check all tubings, fittings, valves, chamber, and columns for leaks or kinks that may block the fluids (see Screen 7.35). In case there is any leakage, restart the process with a new tubing set and medium.

The CentriCult Unit lid unlocks automatically during this process step. If the lid does not unlock automatically, tap the **<open lid>** button on the tool bar (see Screen 7.35). In the event the lid cannot be opened, contact Miltenyi Biotec Technical Support.

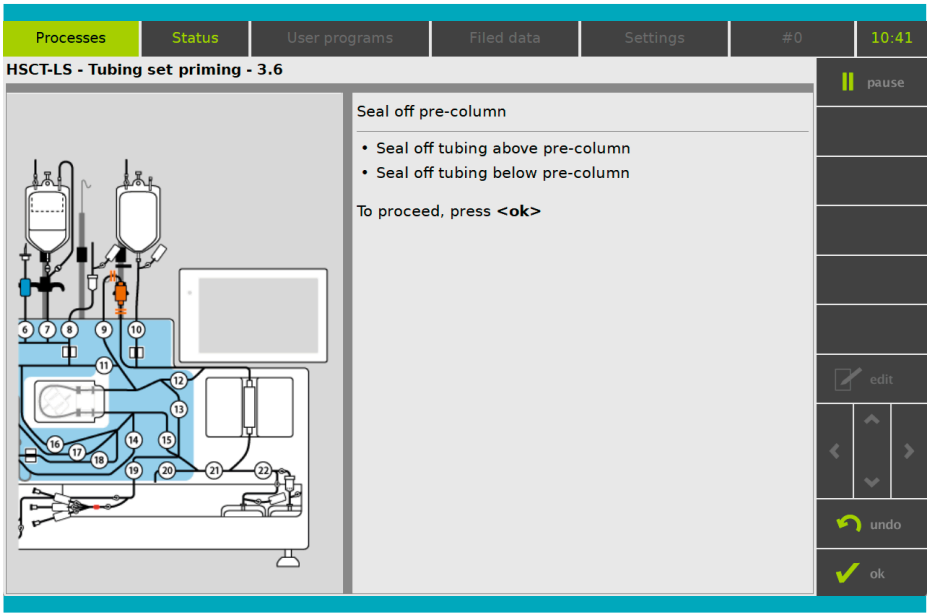


Screen 7.36: End of priming phase

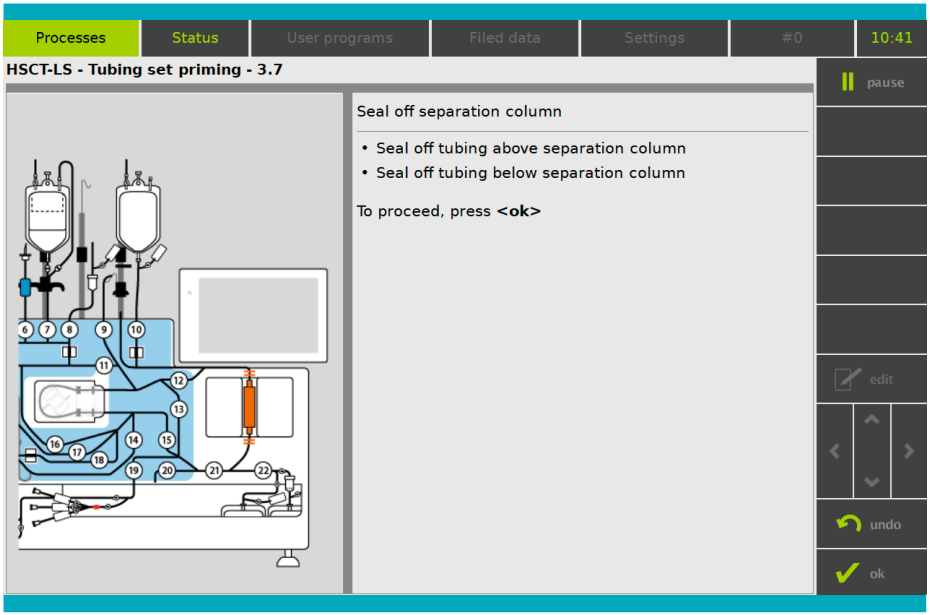
IMPORTANT

It is recommended to perform the tubing set priming not more than 3 hours in advance. The screen will show the remaining time until the process must be continued (see Screen 7.36).

Before proceeding with the cultivation process, make sure to remove the pre-column (see Screen 7.37) and the separation column (see Screen 7.38) with the MACS TubeSealer unit to prevent diffusion of solutions or cells.



Screen 7.37: Removal of pre-column



Screen 7.38: Removal of separation column

8

Cultivation of hematopoietic stem cells

This chapter outlines the procedure to genetically modify HSCs by viral transduction. During preparation, the setup of the HSCT-LS process is programmed including the pre-cultivation and the transduction. Moreover, the cell bag and medium with cytokines are connected to the tubing set. After the final setup check, the HSCT-LS process can be started.

During pre-cultivation, the cells are transferred into the chamber. Depending on the chosen culture setup, washing steps and feed with medium are performed. Afterwards, the procedure of transduction as defined in the activity matrix is performed. All activities are exceuted as programed by the user and can be edited during the process.

Finally, the genetically-modified cells are harvested by the activity "end of culture" followed by deinstallation of the tubing set as described in section 8.6 ´Final handling´.

8.1 General remarks

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 (for example if the instrument is running for 72 hours, a minimum of 80 mL medium must be connected). Each Waste Bag connected to the CliniMACS Prodigy TS 620 has a capacity of five 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 Process setup

This section guides the user step by step through the setup of the pre-cultivation part of the HSCT-LS. This includes the connection of the medium with cytokines to the tubing set, the connection of the cell bag (containing the cellular starting material) to the tubing set, the selection of the culture setup with the entry of cellular parameters, and the entry of CO_2.

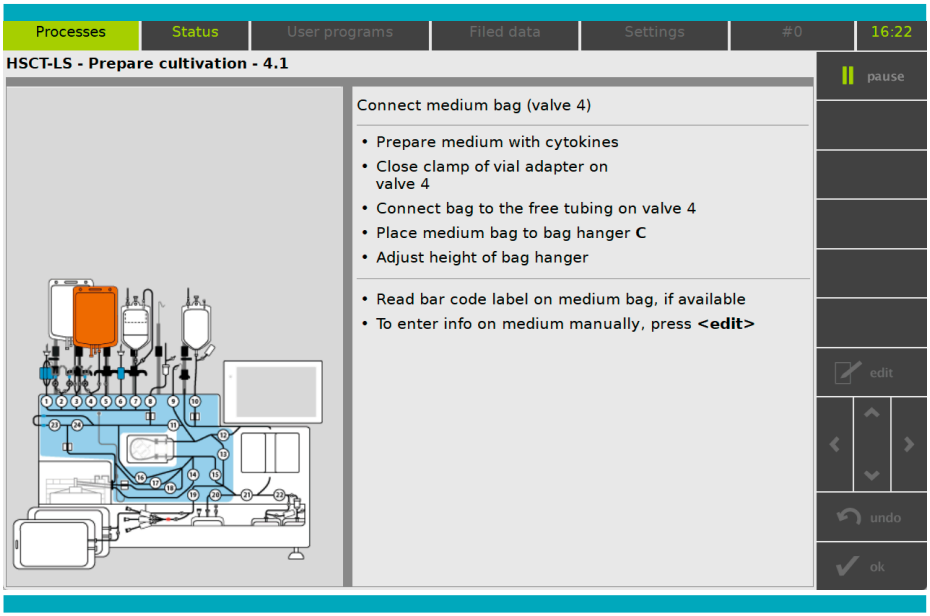
Each screen shows the instructions supported by a picture. If it is required to return to a previous step during the setup, tap **< undo >**.

8.2.1 Connection of medium with cytokines

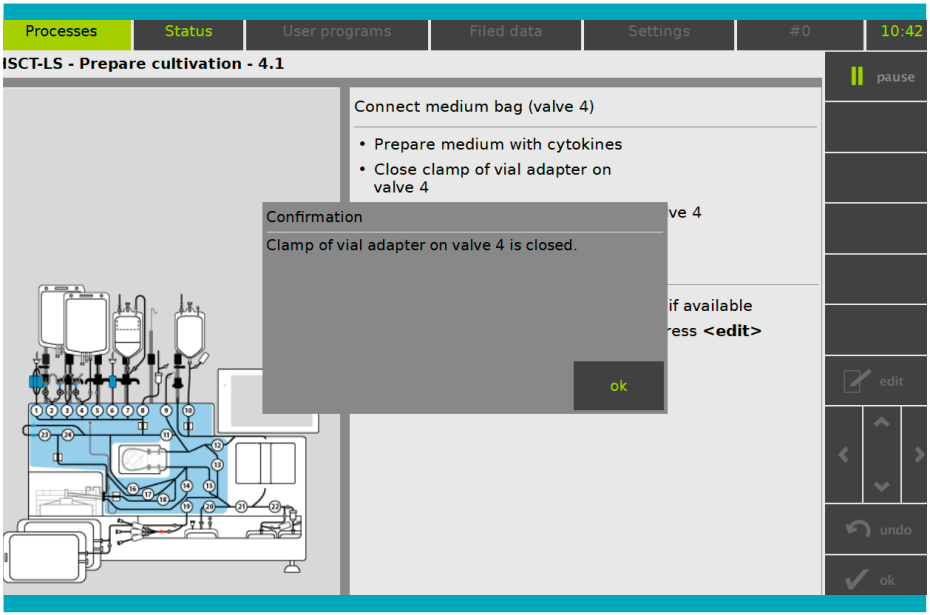
The connection of the medium with cytokines is described in Screen 8.1.

IMPORTANT
Light could lead to adverse effects on the HSC Brew GMP Medium, therefore it should be protected from light.

- Close the clamp to the vial adapter on valve 4.
- To connect the medium bag with cytokines or the free end of the 3-way Tube Adapter (see section 6.3 ´Preparation of medium with cytokines´) to the tubing set on valve 4 by sterile welding, use a sterile tubing welder placed next to the instrument.
- Place the medium bag(s) on bag hanger C.
- Read the barcode label on the medium bag(s) with the barcode reader. Alternatively, tap **< edit >** to enter part number (P/N) and lot number (LOT) manually with the keyboard.



Screen 8.1: Connection of medium bag with cytokines



Screen 8.2: Confirmation of the clamp closure of the vial adapter on valve 4

IMPORTANT

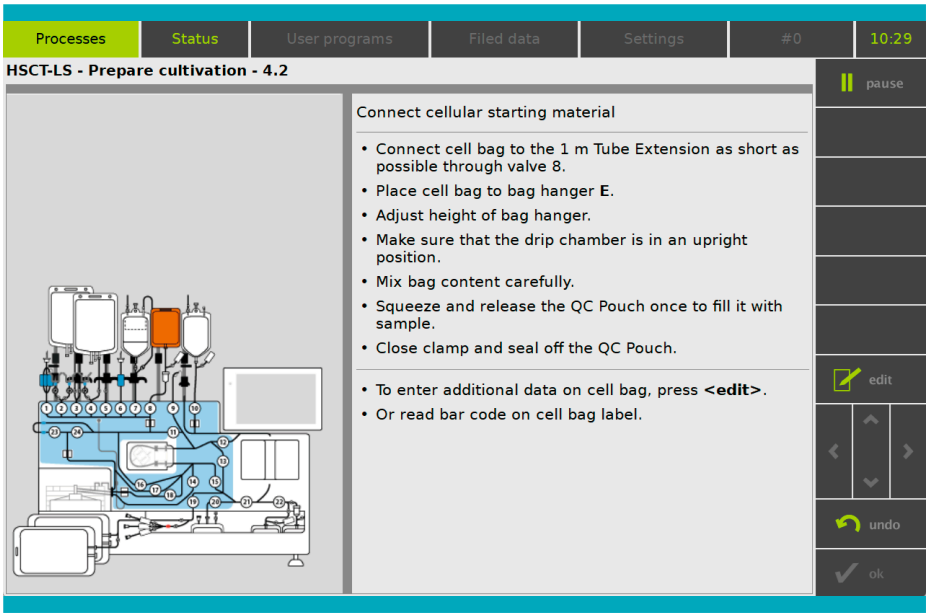
Ensure that all clamps for the medium bag(s) and cell bag are open, and that the tubing of the medium bag(s), the attached 3-way Tube Adapter and the cell bag does not restrict the flow of liquid through the tubing. Ensure that the drip chamber is in upright position and that the content of the cell bag is mixed carefully before sampling.

If necessary, adjust the height of the bag hanger by raising or lowering the hanger. Ensure to position the bag(s) at a suitable height to prevent severe bending or overstretching of the tubing.

8.2.2 Connection of cellular starting material

The cellular starting material for the HSCT-LS process will usually be present in a bag or must be transferred to a bag (termed cell bag). The volume and the concentration of the enriched CD34+ cells must be determined beforehand as described in section 6.1 ´Preparation of cellular starting material´.

For the connection of the cellular starting material, weld the cell bag to the 1 m Tube Extension (see section 7.3.2 ´Installation steps´) by using the sterile tubing welder placed next to the instrument (see Screen 8.3).



Screen 8.3: Connection of cellular starting material

8.2.3 Selection of culture setup and entry of cellular parameters

The culture setup describes the transfer of the cells from the cell bag into the chamber followed by the preparations to start the cultivation.

There are two different culture setup methods that can be chosen: a predefined setup (1) and a flexible setup (2).

Both culture setups include the following steps:

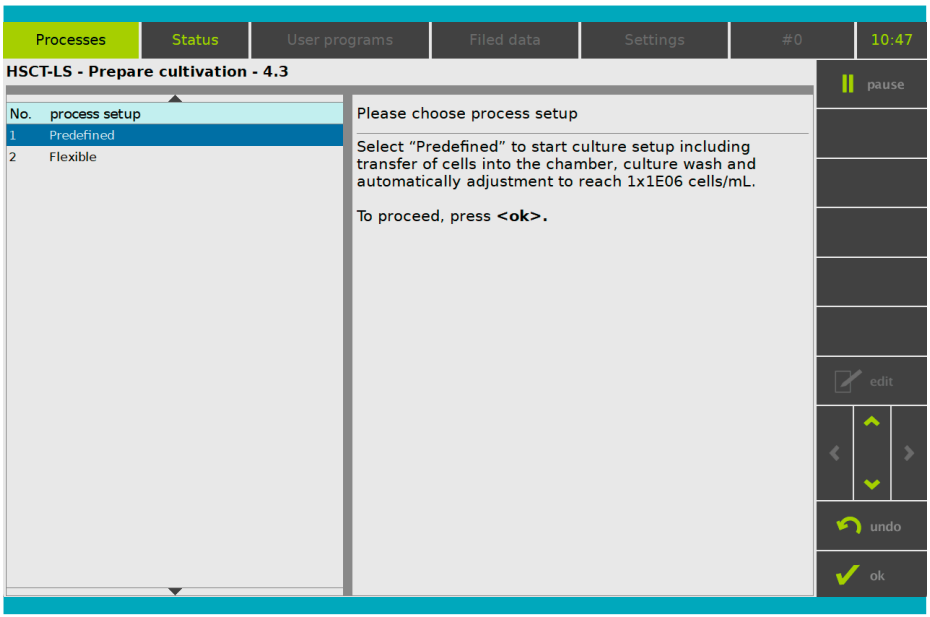
1. Transfer of cells from the cell bag into the chamber.
2. Washing of the cells (in the flexible setup only in case “with wash” is chosen).
3. Volume reduction to 5 mL.
4. Adjustment to the final culture volume with medium including cytokines

The two setups differ in the cell concentration and number of washing steps as detailed below. The predefined culture setup is the recommended procedure.

IMPORTANT
The chosen culture setup is performed in one step and cannot be modified anymore after the process has started (see section 8.4 ´Cultivation´).

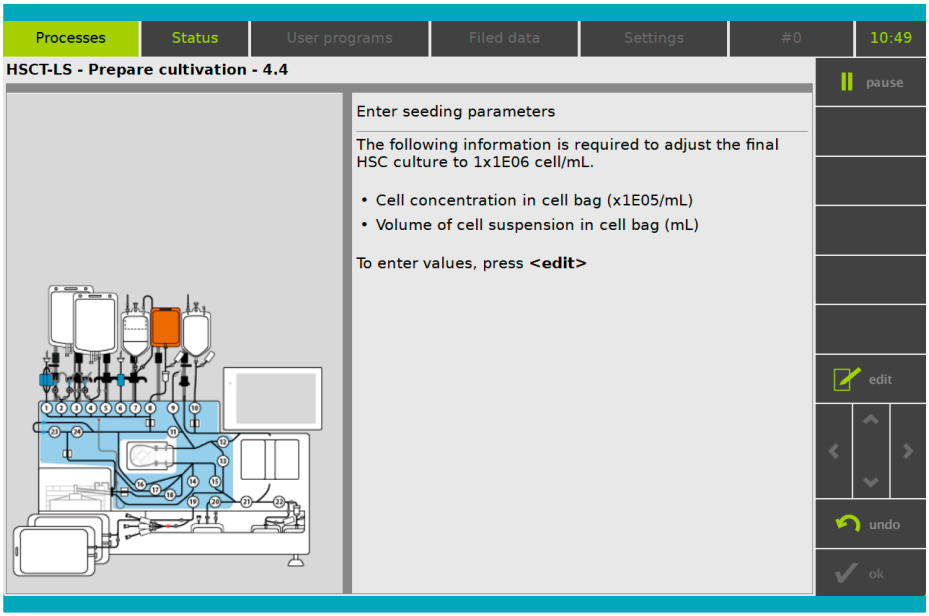
Predefined culture setup

In the predefined culture setup (Screen 8.4), the cells are transferred into the chamber and washed twice with medium without cytokines. After volume reduction to 5 mL, the cell concentration is adjusted to 1×10^6 cells/mL by the addition of medium with cytokines.



Screen 8.4: Selection of process setup "culture setup predefined"

Tap < edit > to enter the concentration and the volume of the cell suspension in the cell bag.

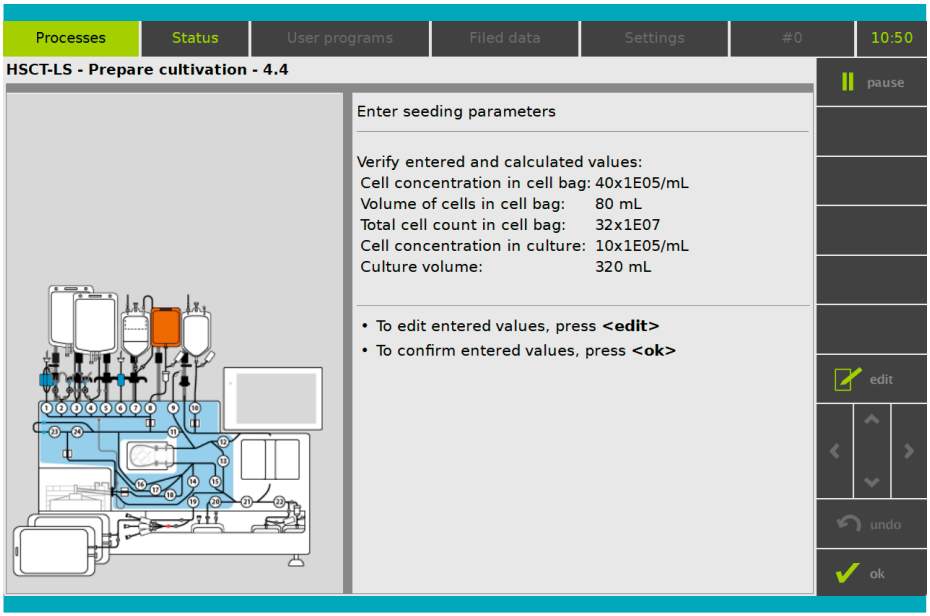


Screen 8.5: Entry of cellular starting material parameters (culture setup predefined)

IMPORTANT

The process must be started with 4×10^7 to 6×10^8 total cells in the cell bag to reach the cell concentration of 1×10^6 cells/mL in the chamber.

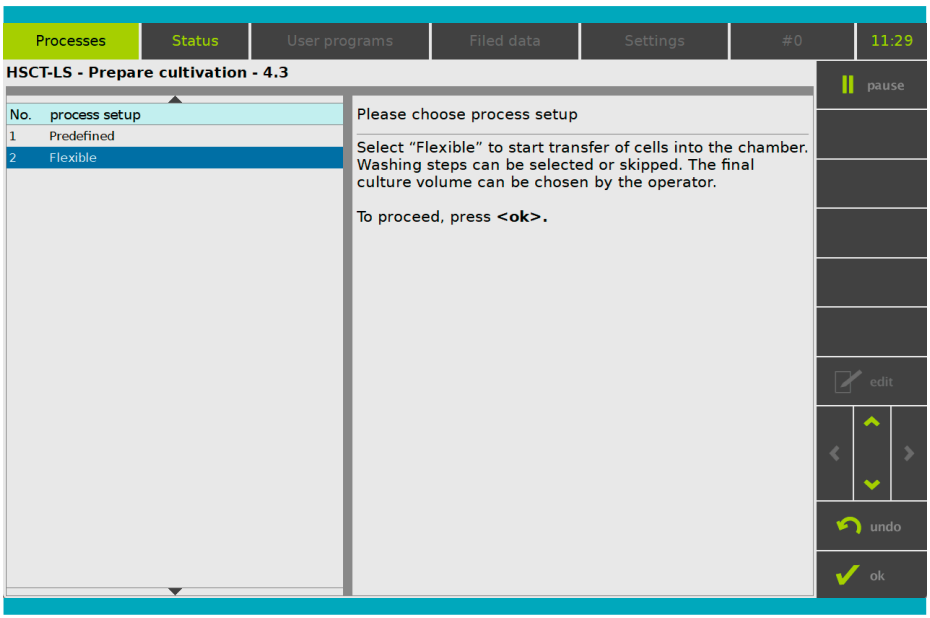
Screen 8.6 shows the entered parameters as well as the calculated values for the total cell count and the resulting culture volume. Review the parameters and edit them if required.



Screen 8.6: Entered and calculated cellular starting material parameters (culture setup predefined)

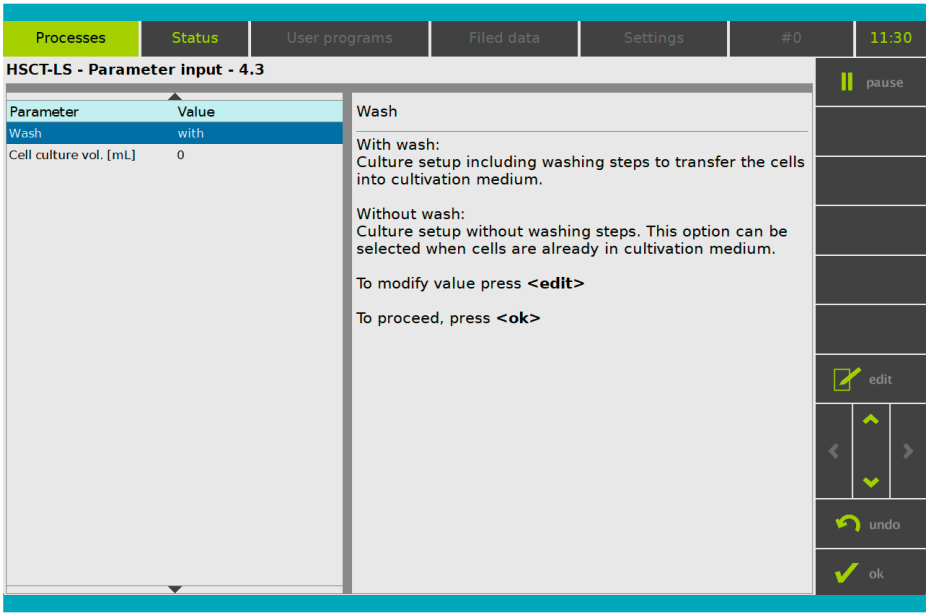
Flexible culture setup

In the flexible culture setup, the washing of the cells can be skipped. The final culture volume can be defined in a range of 40 mL to 600 mL.



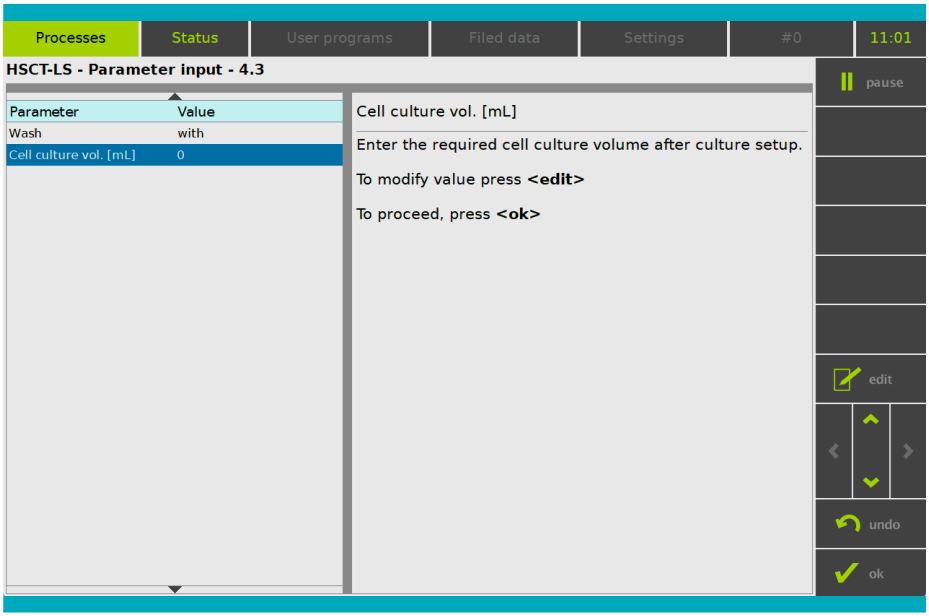
Screen 8.7: Selection of process setup "culture setup flexible"

In Screen 8.8, it is defined if a washing step is needed. If cells are already in medium and do not need to be washed, select without.



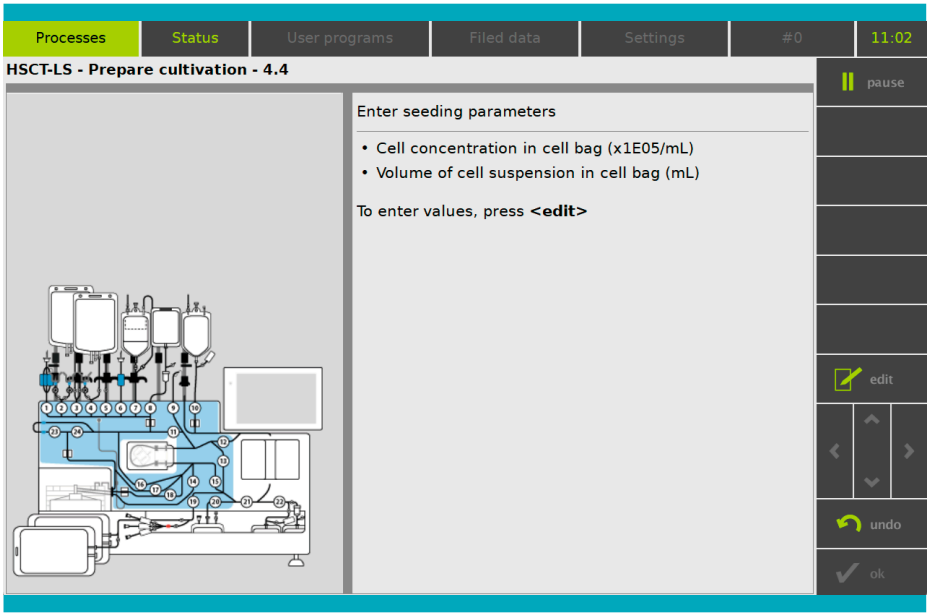
Screen 8.8: Selection of culture setup with or without wash (culture setup flexible)

In Screen 8.9, the required final culture volume can be entered.



Screen 8.9: Selection of the final cell culture volume in the chamber (culture setup flexible)

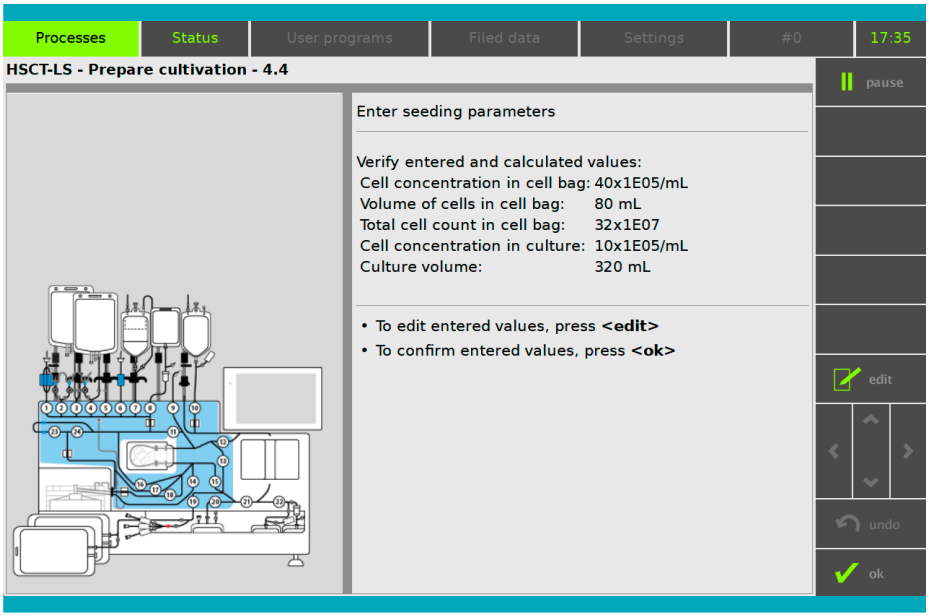
After setting up the flexible culture setup, the cell concentration and the volume of the cell suspension in the cell bag must be entered (see Screen 8.10).



Screen 8.10: Entry of cellular starting material parameters (culture setup flexible)

Screen 8.11 shows the entered parameters as well as the calculated values for the total cell count and the resulting cell concentration.

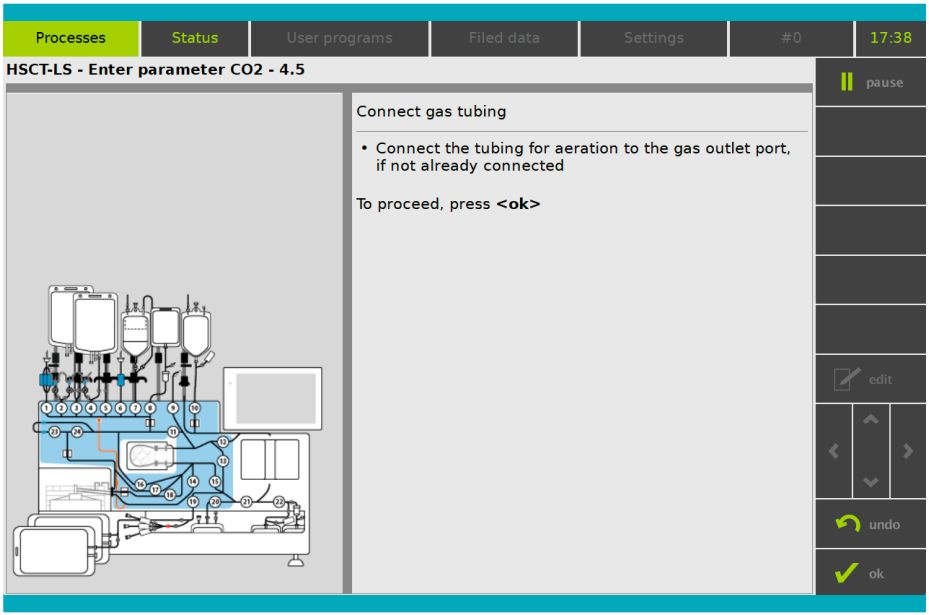
IMPORTANT
Review the parameters and edit them if required.



Screen 8.11: Entered and calculated cellular starting material parameters (culture setup flexible)

8.2.4 Input of CO_2 parameters and automatic temperature set

Ensure that the gas tubing is connected to the gas outlet port of the CliniMACS Prodigy.

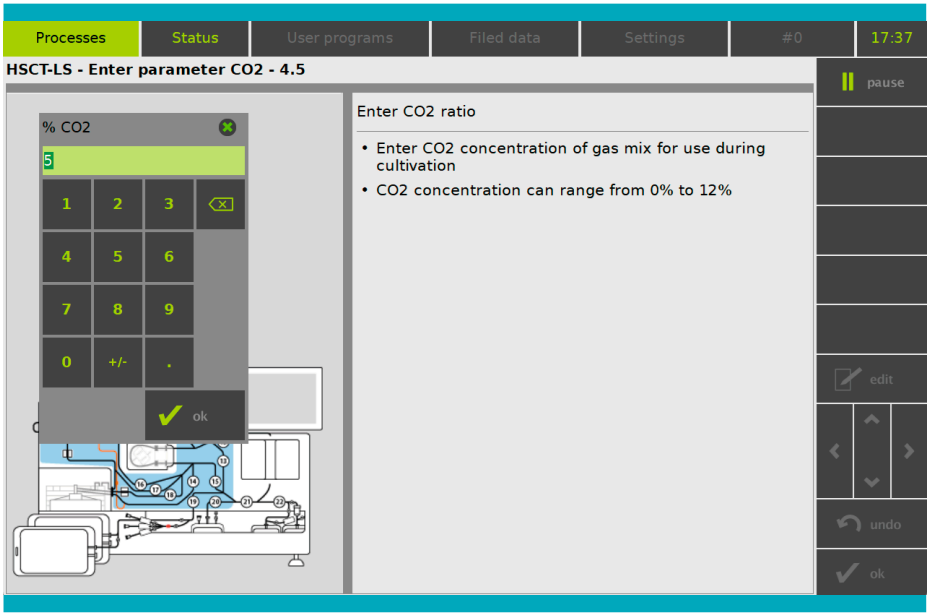


Screen 8.12: Connection of gas tubing

IMPORTANT

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

For cultivation, the concentration of CO_2 in the gas mix must be entered. 5% CO_2 is recommended.



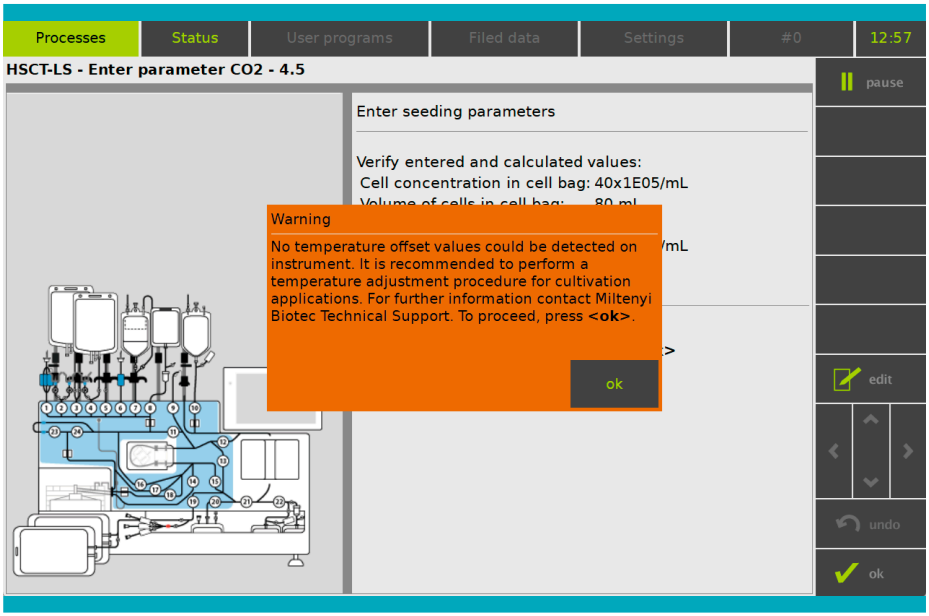
Screen 8.13: Input of CO_2 concentration

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 8.14). 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) (see Screen 8.14).

IMPORTANT

There is no separate screen for entering the temperature. It is automatically set to +37 °C (+99 °F). The Warning only appears if there is no offset value on the instrument.



Screen 8.14: Temperature warning

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

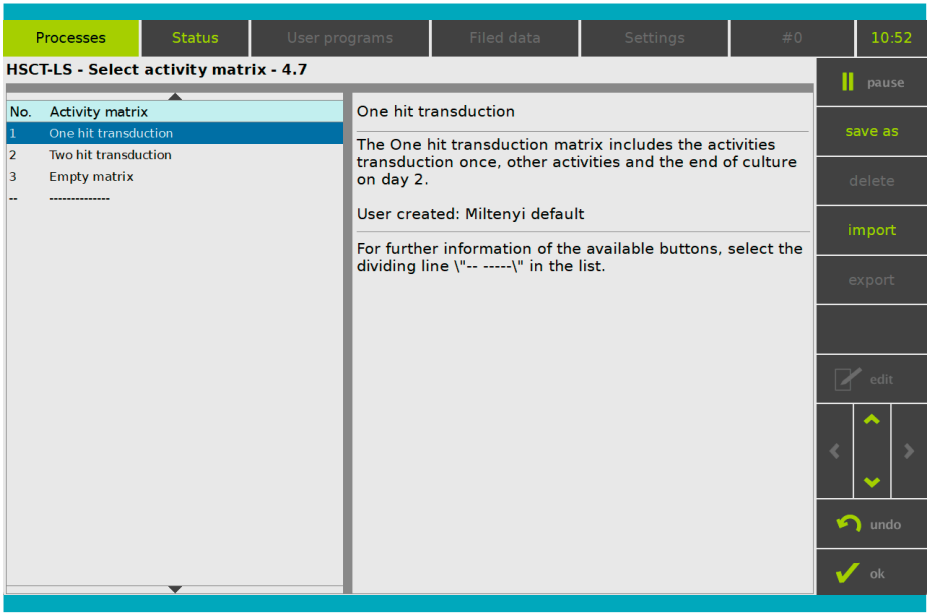
8.3 Setup of activity matrix

The HSCT-LS System allows customized programming of HSC cultivation steps. All HSC cultivation steps are programmed in an activity matrix. This can either be done by choosing a default matrix (see ´Set default matrix´ on page 75) or by creating an individual and permanently saved activity matrix on the CliniMACS Prodigy.

Individually designed activity matrices can be imported and exported across CliniMACS Prodigy instruments (see ´Creation of individual protocols´ on page 77). Each activity matrix can be modified during the cultivation phase, but those changes cannot be saved for future 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 and is not part of the activity matrix. It cannot be modified.

Set default matrix



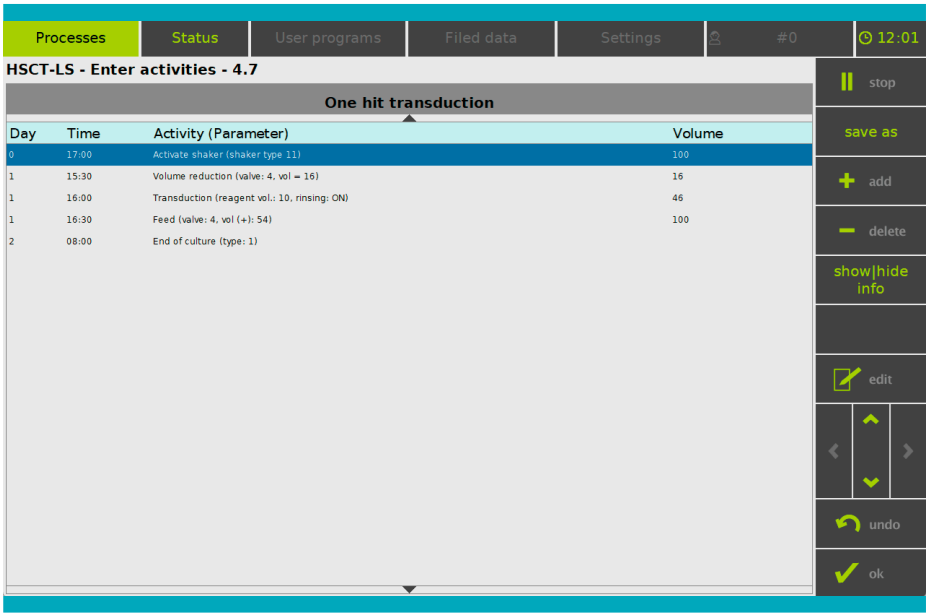
Screen 8.15: Options to setup the activity matrix of the HSCT-LS process

There are three options available.

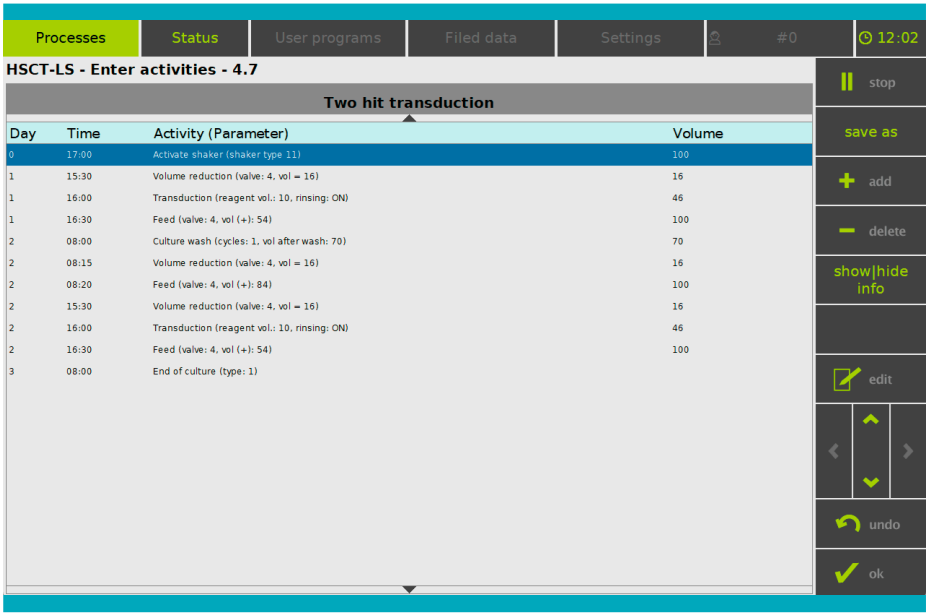
- The “One hit transduction” is a predefined activity matrix with a sequence of activities which programs one transduction round. It can be modified by adding or deleting activities.
- The “Two hit transduction” is a predefined activity matrix with a sequence of activities which programs two transduction rounds. It can be modified by adding or deleting activities.
- The “Empty matrix” is an empty activity matrix for individual programming. All activities must be added manually excluding the activity “end of culture” which can be modified if necessary.

IMPORTANT

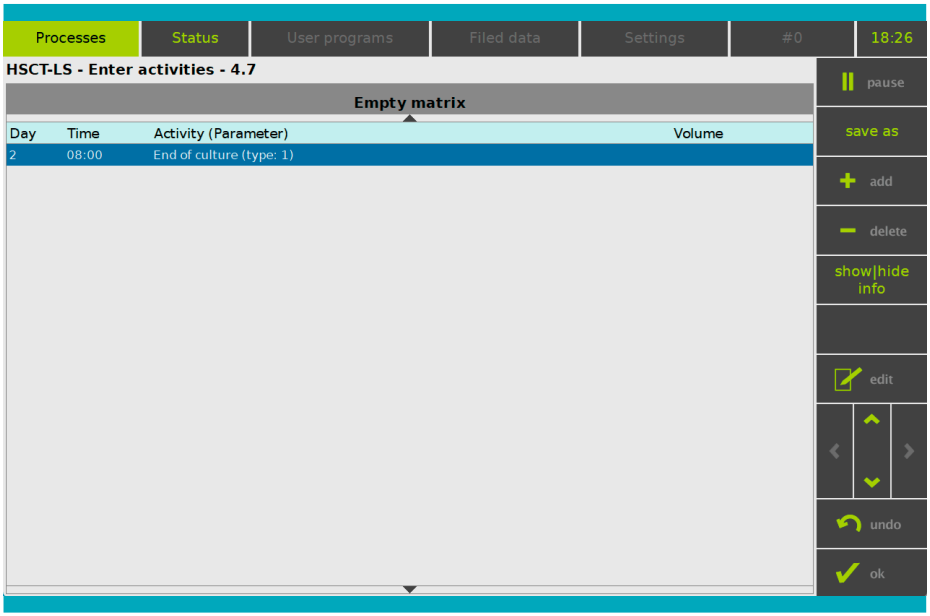
The previously selected culture setup (see section 8.2.2 ´Connection of cellular starting material´) is not listed in the activity matrix. The activity “end of culture” programs the harvest (see 8.5.1 ´End of culture type 1´) and is required as the final activity of the HSCT-LS process. Do not delete the activity “end of culture” from the activity matrix.



Screen 8.16: Activity matrix for one transduction round after selecting "One hit transduction"



Screen 8.17: Activity matrix for two transduction rounds after selecting "Two hit transduction"

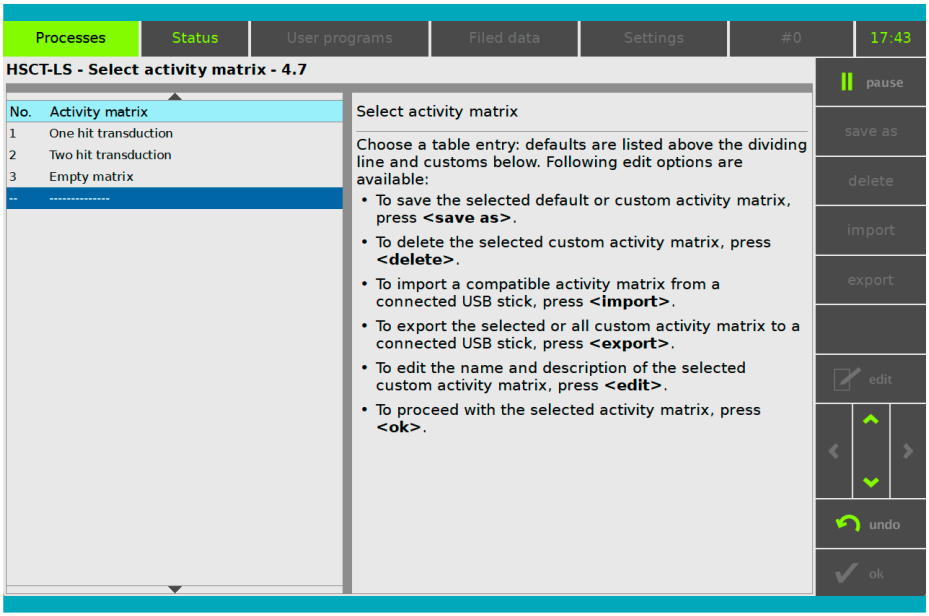


Screen 8.18: Empty activity matrix for individual programming after selecting "Empty matrix"

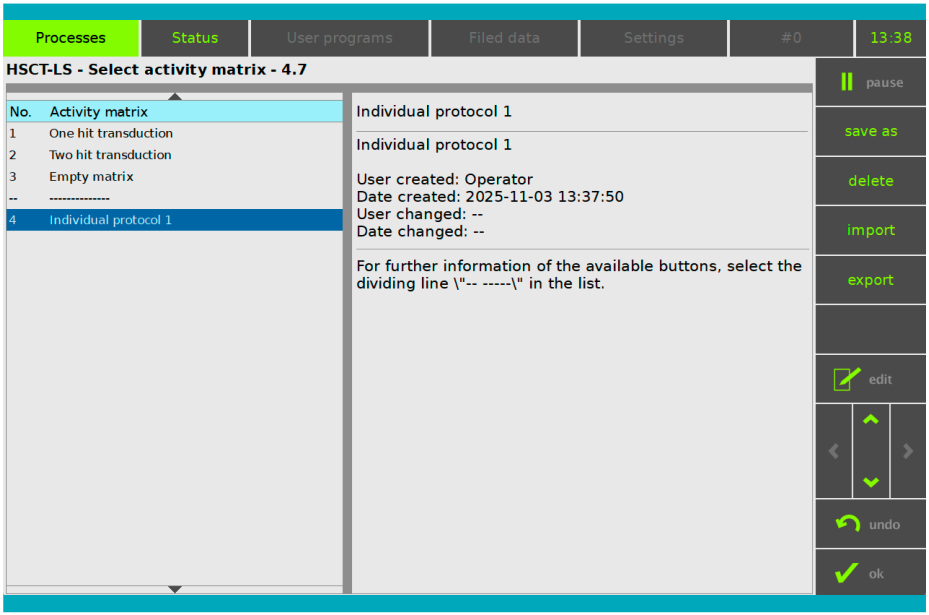
Tap **< show/hide info>** to show extra information on the entered parameters and instructions to edit the activity matrix.

Creation of individual protocols

The user can create individual activity matrices which remain permanently on the CliniMACS Prodigy. For detailed instructions tap the dividing line ("----------") in the list on the left-hand side of the screen (see Screen 8.19).



Screen 8.19: Creation of individually designed activity matrices



Screen 8.20: Creation of individual protocol

To create an individual activity matrix, select a default matrix as template (“One hit transduction”, “Two hit transduction” or “Empty matrix”) and tap <save as>. Rename the new activity matrix with maximal 30 digits and give it an individual description with maximal 300 digits. Special characters are not allowed (for example “Individual protocol 1”).

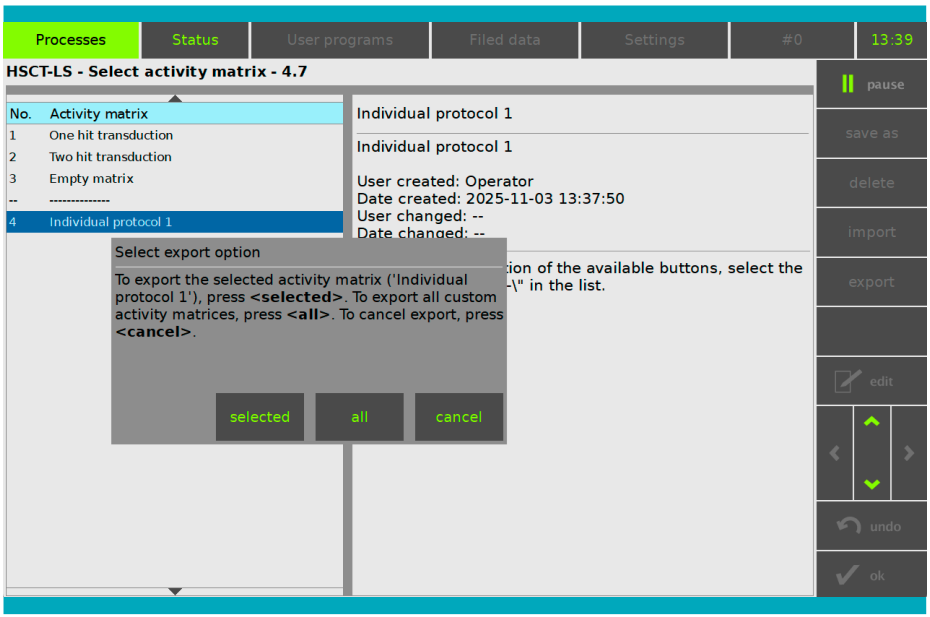
To edit an existing activity matrix, select it from the list and tap <edit> (see Screen 8.20).

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.

IMPORTANT

Do not use the numbering of the matrix as an identifier as the numbering can change if matrices are deleted from the list. The username and the current date will be logged under the description on the right side. Newly created activity matrices can be edited and deleted by tapping <edit> or <delete> .

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



Screen 8.21: Export of individually designed activity matrices

Individual activity matrices can be exported and imported to further CliniMACS Prodigy instruments (see Screen 8.21). 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 among instruments.

Some of the following activities (listed in Table 8.1) have an influence on the volume in the chamber. This volume is theoretically calculated in the activity matrix in the column "Volume" (see Screen 8.16 and Screen 8.17).

The total volume in the chamber must be maintained between 16 mL and 600 mL. If these values are exceeded during the setup of the activity matrix a warning will be shown at the final confirmation step.

IMPORTANT
The HSCT-LS System is only verified for a cultivation time of up to three days.

Available activities for the HSCT-LS Process

Activity	Description	Remark
Activate shaker	Start a continous shaking of the chamber for suspension culture	Countinous in background
Deactivate shaker	Switch off a previously activated shaker	Automatic execution
Culture wash	Wash of culture to remove the transduction reagent and/or the gene modification reagent.	Automatic execution
Volume reduction	Volume reduction of culture volume using centrifugation, e.g., to be used before transduction	Automatic execution
Feed	Add fresh medium	Automatic execution
Media exchange	Remove old medium and add fresh medium with cytokines	Automatic execution
Transduction	Transfer of transduction reagent to chamber	User confirmation/ interaction upon execution required
Gene modification	Transfer of gene modification reagent to chamber	User confirmation/ interaction upon execution required
Temperature change	Change of cultivation temperatue	Continous in background
Spin	Centrifugation step to be used after addition of viral vector for spinoculation protocol or after gene modification agents.	Automatic execution
Medium exchange bag	Request and user guidance to exchange medium bag	User confirmation/ interaction upon execution required
Waste bag exchange	Request and user guidance to exchange waste bag	User confirmation/ interaction upon execution required

Activity	Description	Remark
End of culture	**End of culture type 1:** Cells will be rebuffered in formulation solution and transferred to the Target Cell Bag in a final volume of 100 mL **End of culture type 2:** Cells will be transferred to the Target Cell Bag with an optional fill-up with medium to max. 900 mL **End of culture type 3:** 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:** Cells will be stored in the chamber in the current culture volume at +8 °C (+46 °F) with slow shaking	User confirmation/ interaction upon execution required

Table 8.1: Available activities for the HSCT-LS process

In Screen 8.22 the columns "Day" and "Time" indicate the scheduled point in time for each activity. Time is shown in 24-hour format.

The column "Activity (Parameter)" depicts the activities with their respective parameters:

- Port stands for the valve which will be opened.
- "Vol (+)" stands for the volume which is added through the selected port.
- "Vol =" stands for the desired culture volume in the chamber after performance of the activity.
- "Reagent vol" stands for the volume of the reagent which is added.
- "rinsing: ON" indicates that a rinsing step was chosen.

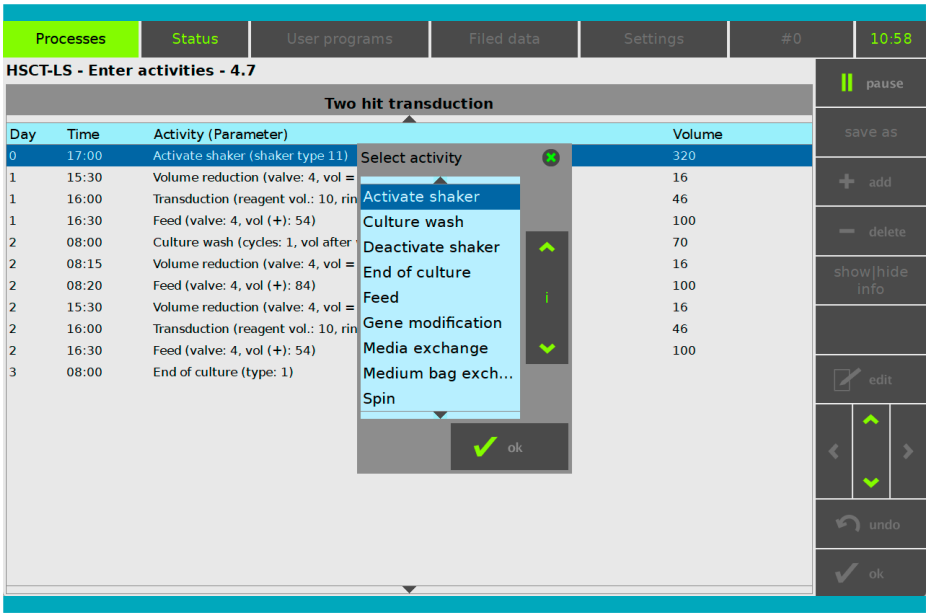
The column "Volume" indicates the expected culture volume in the chamber after the activity has been executed.

IMPORTANT

Volume changes during subsequent activities will be summed up by the instrument software, and the respective value for the volume in the chamber is shown in the column "Volume" of the activity matrix. Every sampling results in a decrease of the chamber volume of up to 3 mL which is not taken into account in the calculation of the shown chamber volume. The total volume inside the chamber must be between 16 mL and 600 mL. If these values are undercut or exceeded, a warning will appear at the final confirmation step. A total culture volume in the chamber of up to 600 mL is recommended for the HSCT-LS process.

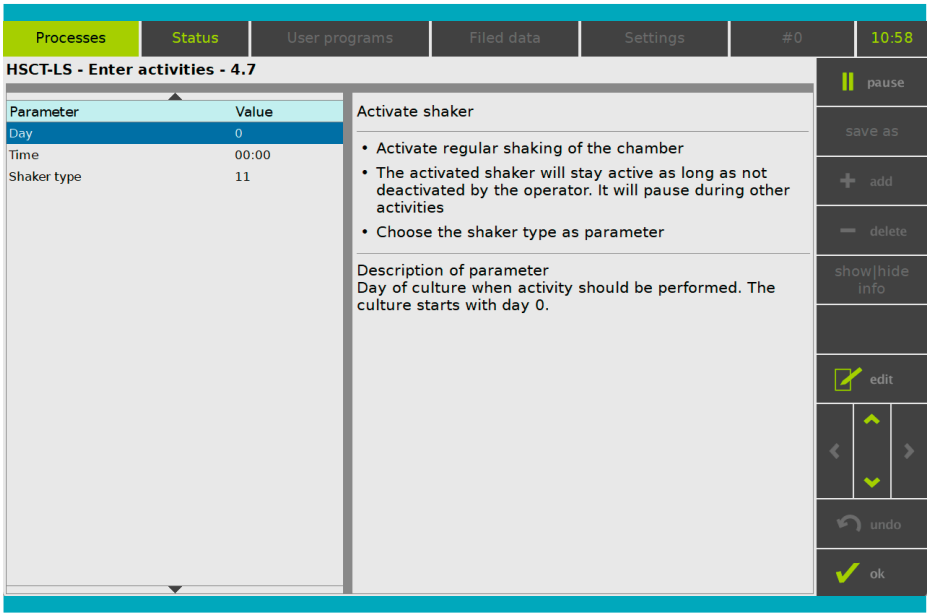
At any step during the setup, tap the <undo> key to return to the previous step.

The selected activity matrix can be modified by adding or deleting activities, or changing the parameters such as day and time of activity execution.



Screen 8.22: Activity matrix – Addition of an activity

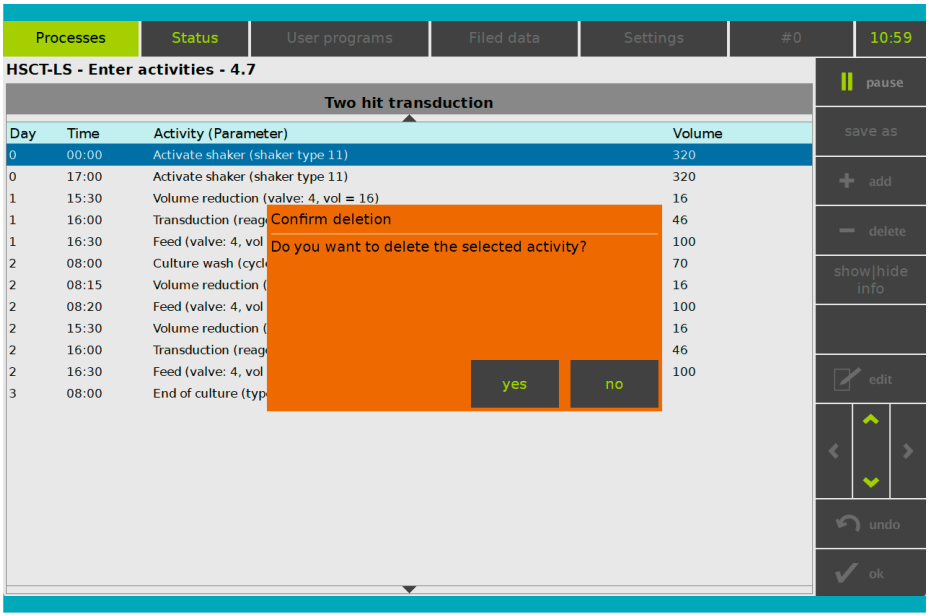
A new activity (see Table 8.1) can be added by tapping <add> and choosing the activity from the drop-down menu. To select the activity tap <ok>.



Screen 8.23: Parameter entry in case of activity addition or editing

A screen specific for the added activity opens, in which all parameters including the day and time of execution and further parameters of this activity can be changed by tapping <edit>. To confirm and return to the matrix, tap <ok>.

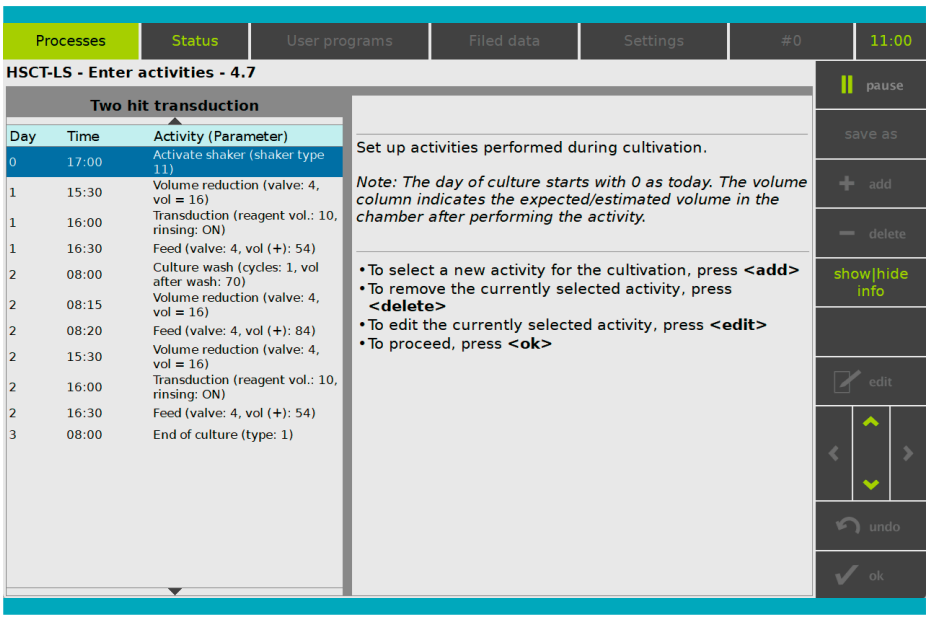
Activities can be edited by selecting the activity (highlighted in blue in the activity matrix, for example shown in Screen 8.22) and tapping <edit>. A screen specific for the selected activity opens, allowing changes of the respective parameters by tapping <edit> (see Screen 8.23).



Screen 8.24: Activity matrix – Deletion of an activity

To delete an activity from the matrix, select this activity (highlighted in blue), tap <delete> and confirm deletion by tapping <yes> (see Screen 8.24).

Tap <show/hide info> to show the instructions on how to edit the activity matrix (see Screen 8.25).

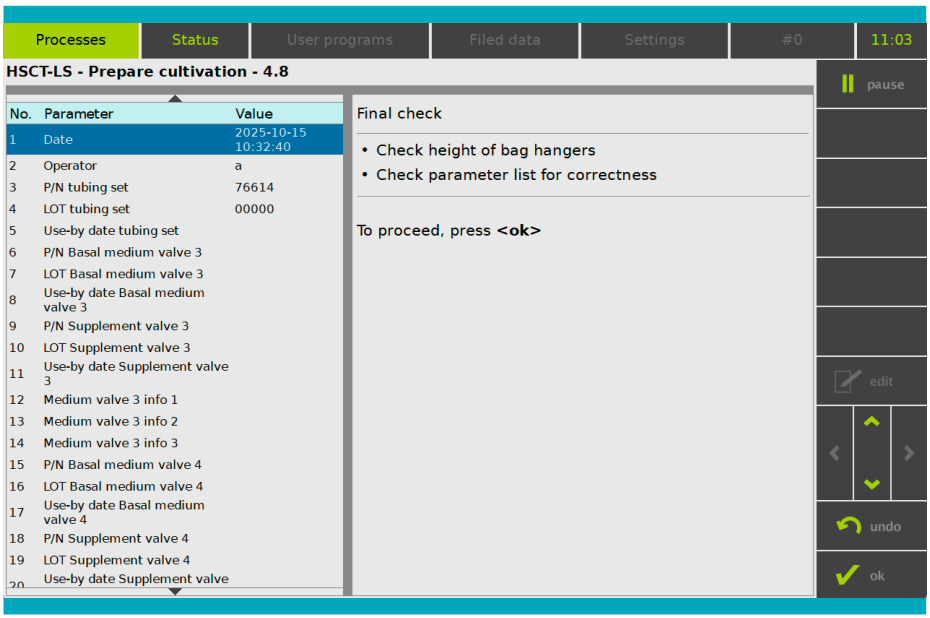


Screen 8.25: Activity matrix – Instruction on editing the matrix

8.3.1 Final check before process start

The user is asked to check the height of the bag hangers and the vial holders as well as the parameter list (see Screen 8.26).

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



Screen 8.26: Final check of the cultivation setup

At this point, all preparative steps are complete, and the automated cultivation process can begin. Press <ok> to proceed. Press <yes> to confirm the set up. The automated culture set up is initialized.

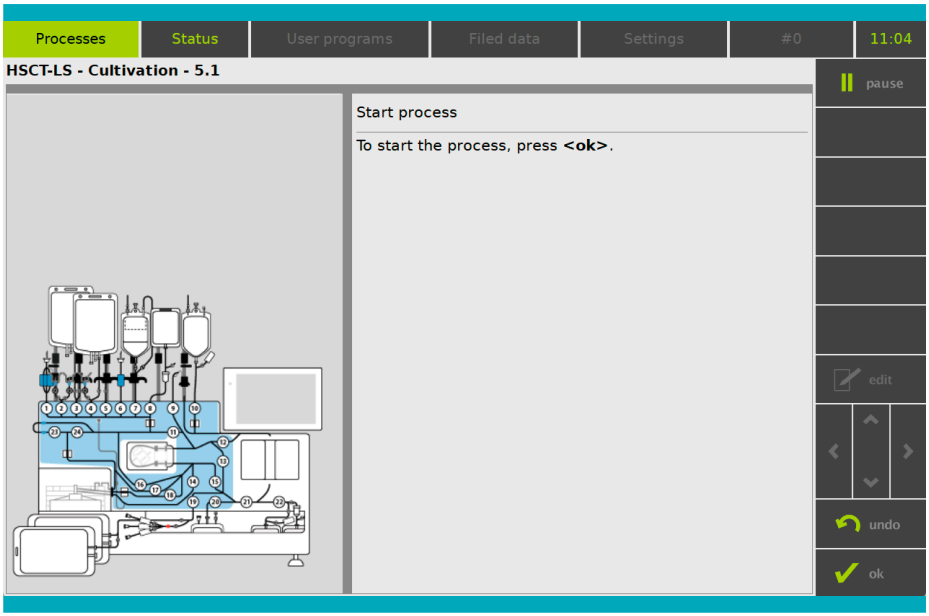
8.3.2 Automated culture setup

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

1. Transfer of the cells from the cell bag to the chamber.
2. Rinsing of the call bag and transfer to the chamber.
3. Washing of the cells with medium (in case culture setup predefined or flexible with wash was selected).
4. Volume Reduction.
5. Fill up with medium including cytokines to the desired culture volume.
6. Setup of aeration and temperature.

IMPORTANT

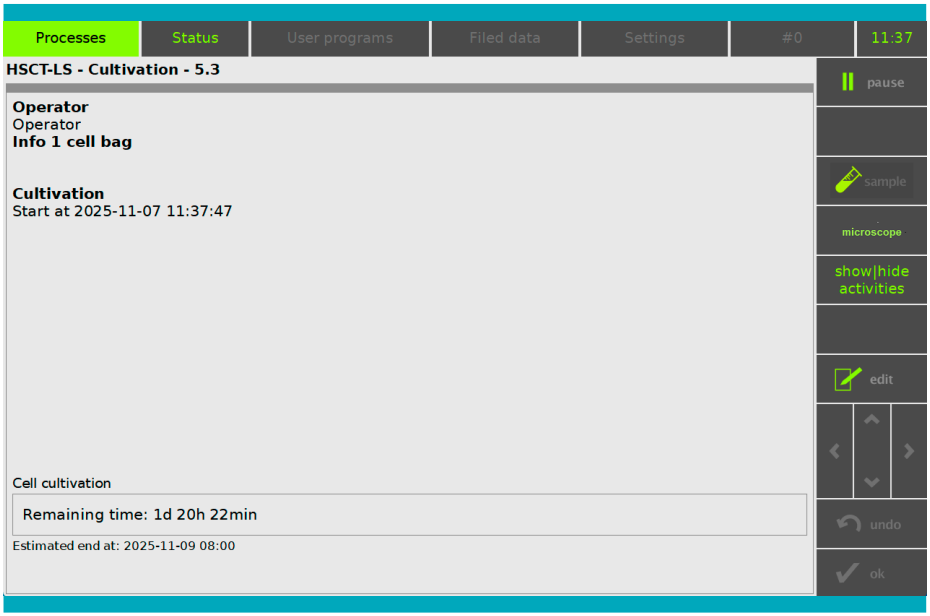
All steps programmed in the activity matrix are performed after the automated culture setup. The culture setup is performed automatically in one step and is not part of the activity matrix.



Screen 8.27: Start of automated culture setup

8.4 Cultivation

As described in section 8.3.2 ´Automated culture setup´, the activity matrix can be edited during execution by tapping **<edit>**. To show the current activity matrix, tap the **<show/hide activities>** button. Do not tap the **<stop>** button, unless you want to abort the process.

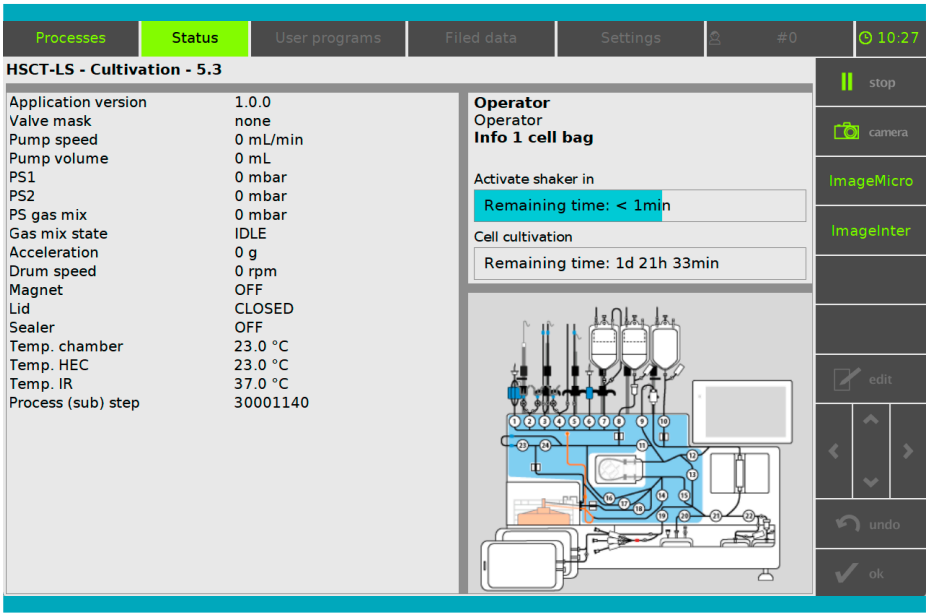


Screen 8.28: HSCT-LS process

IMPORTANT

The activity matrix can be adapted during the running process. As soon as the selected time (shown in column "Time") is reached, the activity will be started. No adaptation of the activity matrix is possible as long as an activity is performed.

The <Status> screen shows the current activity and the remaining time of the process.



Screen 8.29: HSCT-LS – Status screen

The following section describes the monitoring possibilities via sensor values (see section 8.4.1 ´Monitoring via sensor values´), sampling (see section 8.4.2 ´Sampling using the QC pouch accessories´) and photographic recording (see section 8.4.3 ´Taking microscope pictures´) during the HSCT-LS process. The harvest by the activity "end of culture" is described in section 8.5 ´End of culture´.

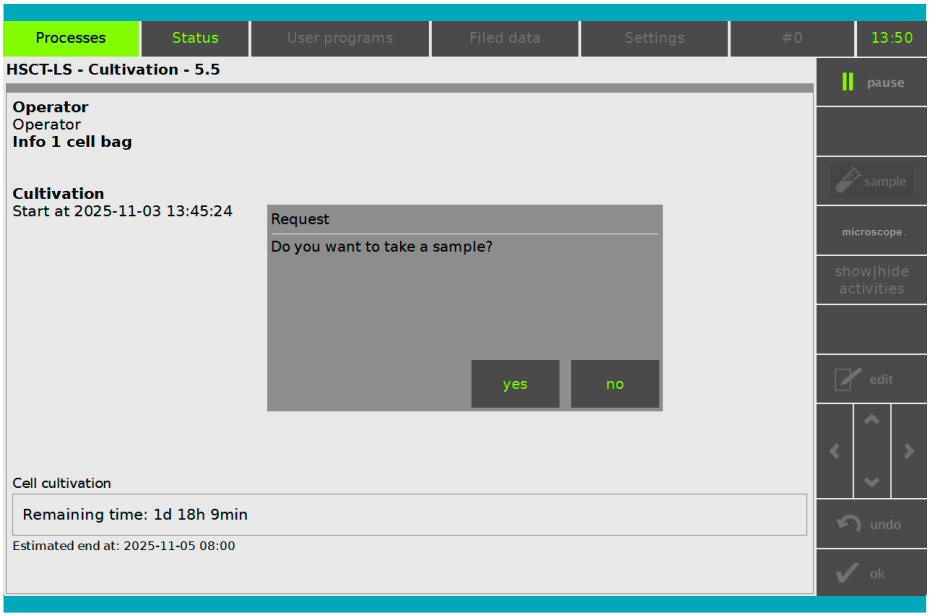
Refer to section 8.4 ´Cultivation´ for detailed information on all other activities of the HSCT-LS process.

8.4.1 Monitoring via sensor values

During the cultivation, several sensor values can be monitored on the <Status> screen as shown in Screen 8.29. The pressure sensor "PS gas mix" is inside the gas mix unit and must show values between 0 mbar and 800 mbar during the setup and between 200 mbar and 800 mbar during cultivation.

8.4.2 Sampling using the QC pouch accessories

To take a sample from the chamber during cultivation, change to the <Processes> screen, tap <sample> and confirm by tapping <yes>. Follow the instructions in the pop-ups leading through the sampling procedure (see Screen 8.30).



Screen 8.30: Taking a sample

IMPORTANT

When the instructions mention to open/close the clamp leading to the sampling pouches, be aware that actually two clamps need to be opened/closed. Hold the sampling pouch with the sterile filter facing up while the sampling procedure is performed to prevent filter clogging.

After the sampling is completed, close the clamp and weld off the pouch. The sample can be collected by unscrewing the sterile filter.

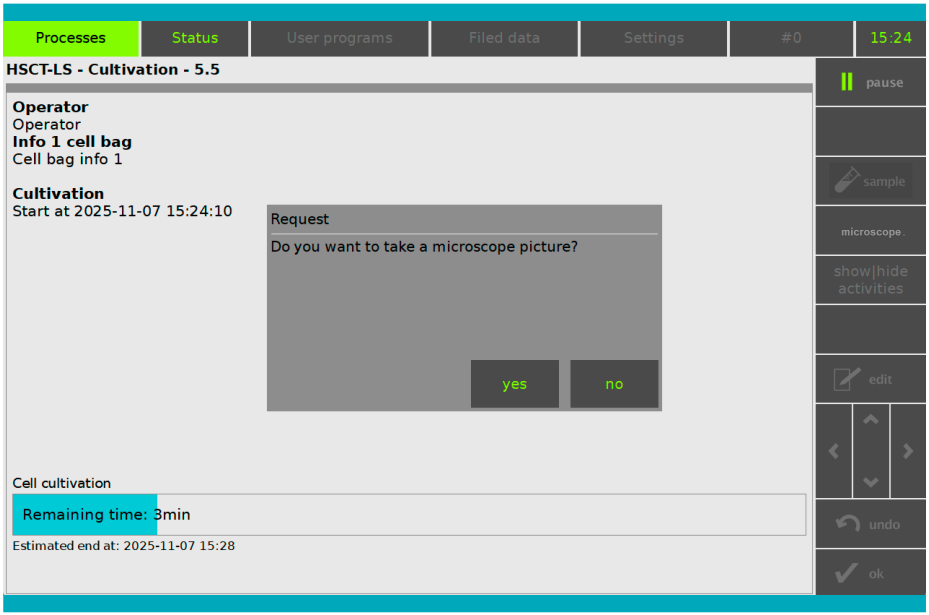
To remove the residual sample liquid from the tubing after the sample has been taken, perform the following steps:

1. Open all clamps from one empty sample pouch leading to the Waste Bag.
2. Squeeze the sample pouch to tap residual liquid to the Waste Bag.
3. Close the sample pouch assembly and the clamp of the sample pouch.
4. Remove the blue cap on the filter of the used sample pouch to release the vacuum.
5. Reinstall the cap.

If more than three samples are required weld on another Triple Sampling Adapter using a sterile tubing welder.

IMPORTANT
Every sampling results in a decrease of the chamber volume of up to 3 mL. Do not remove the sterile filter during sampling as it could result in a contamination of the cell product.

8.4.3 Taking microscope pictures



Screen 8.31: Taking microscope pictures

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 (50-500) for the picture.
- Now the camera will autofocus and take a picture.
- Switch to <Status> screen and select <camera> 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.

IMPORTANT
At higher culture volumes and during agitated culture (with an active shaker) the quality of the picture might decrease due to the light dispersion and because the cells are in suspension and not settled on the bottom of the chamber.

8.4.4 Activate and deactivate shaker

Shaking of the chamber is activated by the activity "activate shaker". It will stay active until deactivated by the activity "deactivate shaker". Shaking is paused during the execution of another activity but continues as soon as the activity is terminated. There are nine different shaker types (see Table 8.2). For the HSCT-LS process, shaker type 11 is recommended.

Shaker types	Perfomance
4	Continous spin (80 rpm), recommended for culture volumes below 40 mL
5	Continous slow spin (4 rpm)
6	3 s 200 rpm, 15 s pause, change of direction
7	3 s 300 rpm, 17 s pause, change of direction
8	3 s 300 rpm, 10 s pause, change of direction
9	3 s 300 rpm, 8 s pause, change of direction
10	3 s 300 rpm, 3 s pause, change of direction
11	3 s 300 rpm, one direction, 30 s pause
12	3 s 300 rpm, one direction, 2 min pause

Table 8.2: Different shaker types with the corresponding parameters

8.4.5 Volume reduction

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

Use the activity "Volume reduction" to reduce the medium in the chamber. For target volumes smaller than 40 mL, the chamber volume is first reduced to 5 mL and afterwards adjusted to the target volume by addition of medium with cytokines. Therefore, confirm there is sufficient medium with cytokines connected to valve 4. For the cultivation in volumes below 40 mL use shaker type 4.

IMPORTANT
The activity "Volume reduction" will be executed automatically. Confirm that there is medium connected to valve 4. The minimal target volume is 16 mL.

8.4.6 Transduction

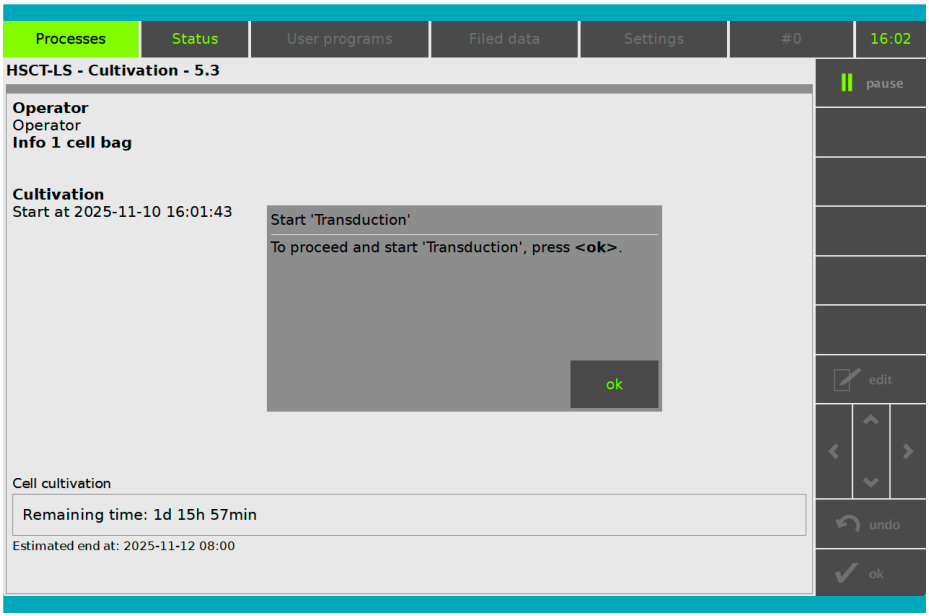
Use the activity "Transduction" to transfer the transduction reagent into the chamber.

If rinsing is chosen, the tubing set and the transduction reagent bag will be rinsed with 20 mL medium with cytokines.

IMPORTANT
Ensure there is sufficient medium in the medium bag connected to valve 4. Use the activity "medium bag exchange" to connect a new medium bag if required.

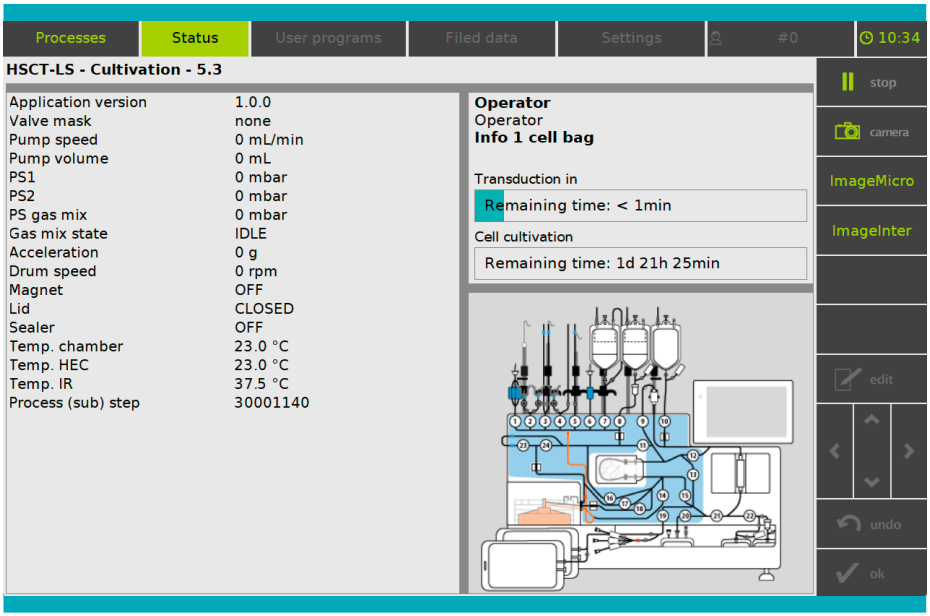
If no rinsing step is chosen, there is still some medium needed for the rinsing of the tubing set after transferring the vector to the chamber. Therefore, sufficient medium needs to be connected at all times.

As soon as the scheduled time of the activity "Transduction" is reached, user interaction is required (see Screen 8.32).



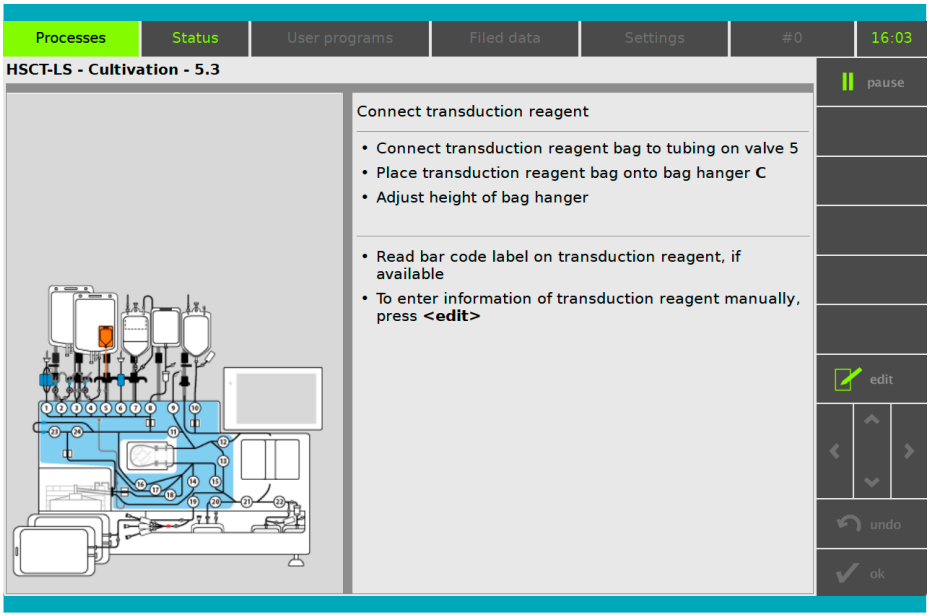
Screen 8.32: Start of the activity "Transduction"

The <Status> screen shows the activity "Transduction" and the remaining time of the process.

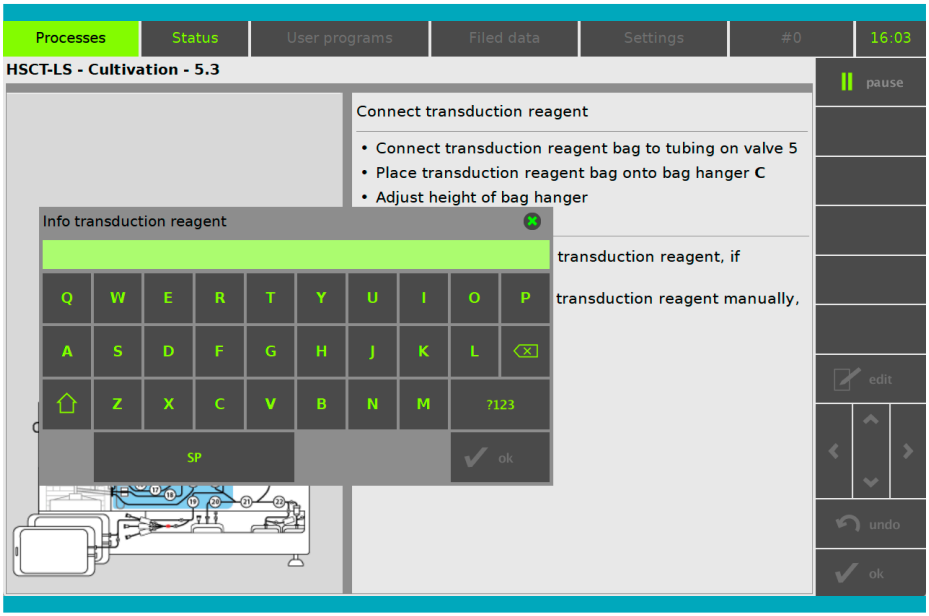


Screen 8.33: Transduction status

After switching to the <Processes> screen, the instructions to connect the transduction reagent bag on valve 5 are shown.



Screen 8.34: Connection of transduction reagent



Screen 8.35: Entering information on the transduction reagent

Read the barcode on the transduction reagent bag or tap <edit> and enter information on the transduction reagent by using the keyboard shown on the screen.

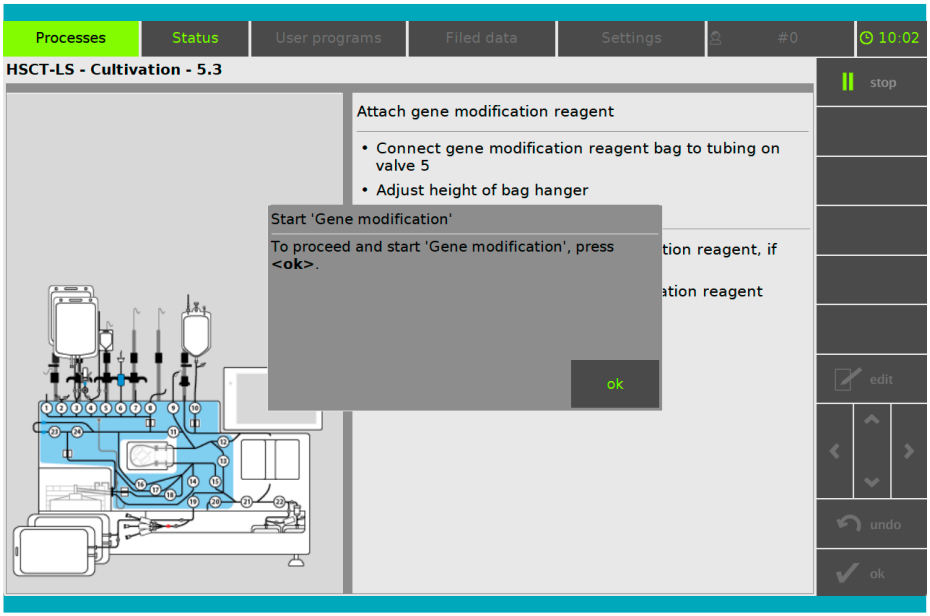
IMPORTANT
Ensure that all clamps for the medium bag(s) and transduction reagent bag are open, and that the tubing of the medium bag(s), the attached 3-way Tube Adapter and the transduction reagent bag do not restrict the flow of liquid through the tubing.

8.4.7 Gene modification

Use the activity "gene modification" to transfer the gene modification reagent into the chamber. If rinsing is chosen, the tubing set and the reagent bag will be rinsed with 20 mL medium with cytokines.

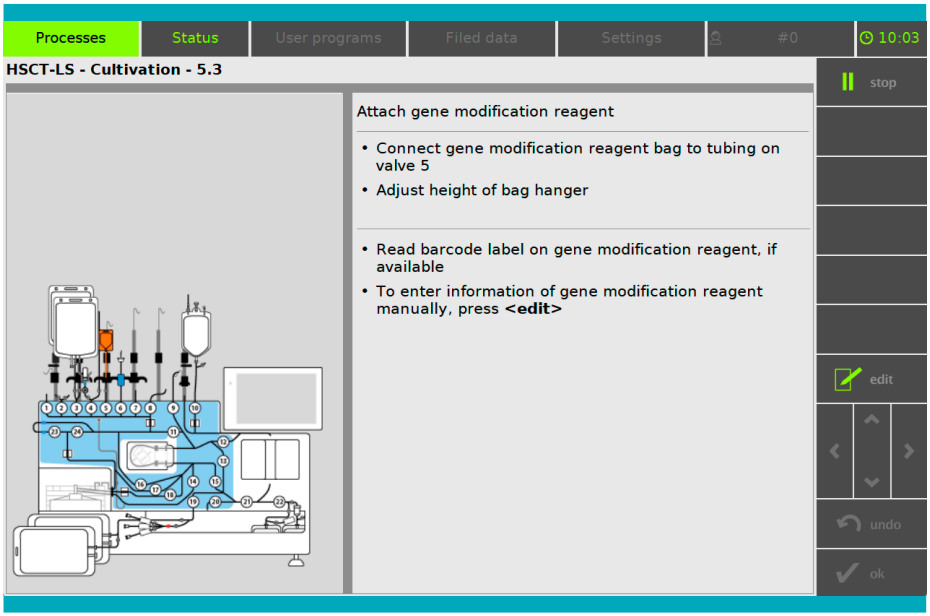
IMPORTANT
Ensure there is sufficient medium in the medium bag connected to the tube through valve 4 in case the rinsing step is chosen. Use the activity "Medium bag exchange" to connect a new medium bag if required. In case you would like to setup a protocol contact Miltenyi Biotec Technical Support.

As soon as the scheduled time of the activity "Gene modification" is reached, user interaction is required.

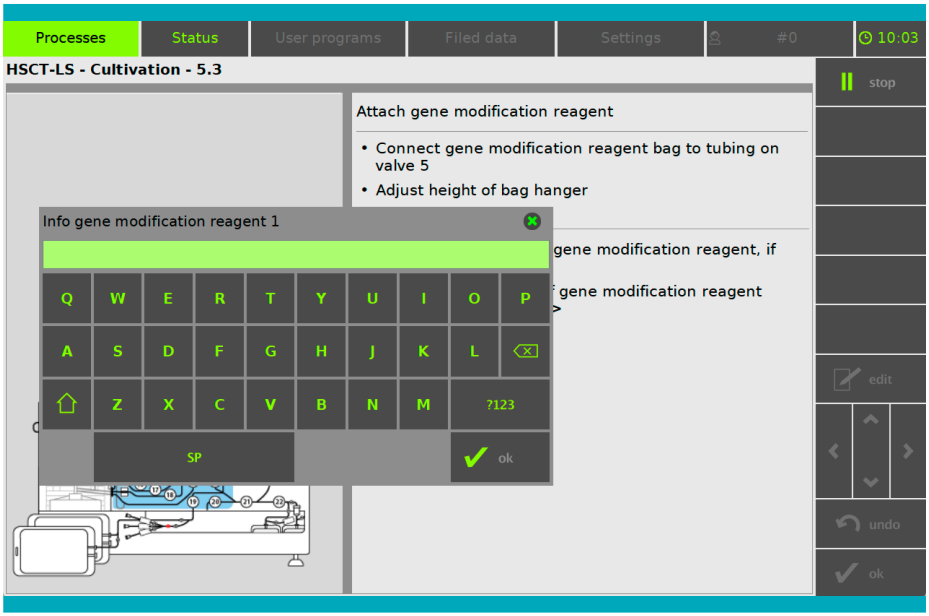


Screen 8.36: Start of the activity "gene modification"

After switching to the <Processes> screen, the instructions to connect the gene modification reagent bag on valve 5 are shown (see Screen 8.37).



Screen 8.37: Connection of gene modification reagent



Screen 8.38: Entering information on the gene modification reagent

Read the barcode on the gene modification reagent bag or tap <edit> and enter information on the gene modification reagent by using the shown keyboard (see Screen 8.38).

IMPORTANT
Ensure that all clamps for the medium bag(s) and gene modification reagent bag are open, and that the tubing of the medium bag(s), the attached 3-way Tube Adapter and the gene modification reagent bag do not restrict the flow of liquid through the tubing.

8.4.8 Feed

Use the activity "Feed" for the addition of fresh medium with cytokines into the chamber, for example to increase the culture volume after the activity "Transduction". The activity "Feed" will be executed automatically.

IMPORTANT
Confirm there is sufficient medium with cytokines in the medium bag connected to the tube through valve 4. Use the activity "Medium bag exchange" to connect a new medium bag if required. Ensure that there is always medium connected to valve 3 for the tubing set rinsing which is automatically performed every 10 hours.

8.4.9 Culture wash

Use the activity "Culture wash" to wash the culture. The amount of medium needed for the culture wash depends on the number of washing cycles programmed into the activity. The washing of the cells is performed with medium from port 3, whereas medium including cytokines from port 4 is used for the final fill-up. The activity "Culture wash" will be executed automatically.

IMPORTANT
Confirm that there is enough medium connected to the tube through valve 3 and 4. Use the activity "Medium bag exchange" to connect a new medium bag if required. In protocols with multiple transduction rounds (for example protocol for two hits, see Screen 8.17) the activity "Culture wash" is used to reduce vector from the first transduction round. In protocols with one transduction round, the vector will be reduced by the washing steps included in the end of culture type 1 and 3 (see section 8.5 ´End of culture´). If end of culture type 2 or 4 is chosen or a higher washing efficiency is required, the activity "Culture wash" can be added before the activity "End of culture". The number of viral particles at the end of culture will depend on the multiplicity of infection (MOI) of the transduction reagent and the number of transduction rounds. It is the responsibility of the user to ensure adequate reduction of the transduction reagent in their respective protocol.

8.4.10 Media exchange

Use the activity "Media exchange" to replace old with fresh medium. Confirm that there is sufficient medium with cytokines in the medium bag connected to the tube through valve 4. Use the activity "Medium bag exchange" to connect a new medium bag if required. The activity "Media exchange" will be executed automatically.

8.4.11 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 8.14). In this case the temperature parameter cannot be guaranteed. For further information contact Miltenyi Biotec Technical Support.

The activity "Temperature change" will be executed automatically. 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.

8.4.12 Spin

Spinoculation might be used to enhance transduction efficiency by spinning the cells and virus. During spinoculation, cells are centrifuged at 2500 rpm and the temperature can be adjusted between +18 °C to +39 °C (+64 °F to +102 °F). The activity "Spin" will be executed automatically.

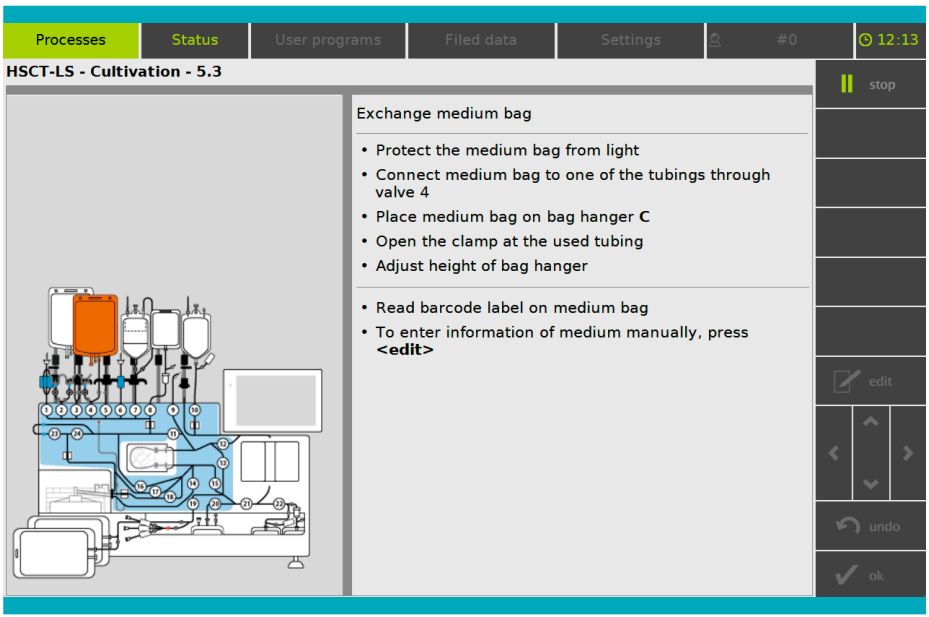
IMPORTANT

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 Screen 8.14). In this case the temperature parameter cannot be guaranteed. For further information contact Miltenyi Biotec Technical Support.

8.4.13 Medium bag exchange

Use the activity "Medium bag exchange" to connect a new medium bag. The valve for the desired medium bag can be chosen. Select valve 3 for the medium bag without cytokines and valve 4 for the medium bag including cytokines.

Refer to section 6.2 ´Preparation of medium´ for the preparation of medium and section 7.4.1 ´Connection of medium´ or section 8.2.1 ´Connection of medium with cytokines´ for more details on the connection of medium via 3-way Tube Adapter. When the programmed time for the activity "Medium bag exchange" is reached, user interaction is required.



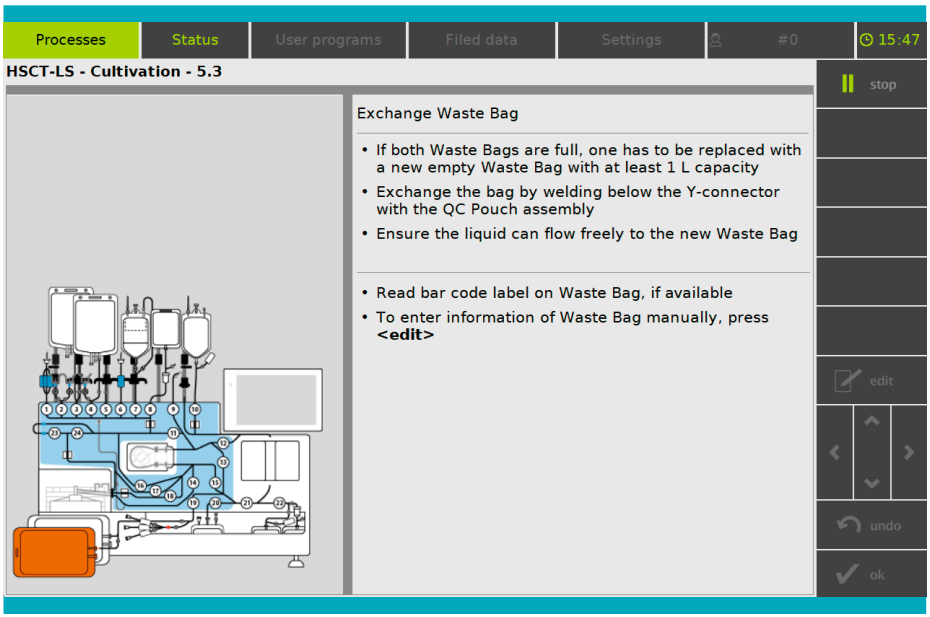
Screen 8.39: Activity "Medium bag exchange"

After switching to the <Processes> screen, follow the instructions on the screen to connect a new medium bag (see Screen 8.39).

Read the barcode on the medium bag or tap <edit> to manually enter the information. Tap <ok>. Enter information regarding supplements by tapping <edit>. Confirm entered values with <ok> to complete the activity and return to the overview of the activity matrix.

8.4.14 Waste bag exchange

Use the activity "Waste bag exchange" to connect a new waste bag. When the programmed time for the activity "Waste bag exchange" is reached, user interaction is required.



Screen 8.40: Activity "waste bag exchange"

After switching to the <Processes> screen, follow the instructions on the screen to connect a new waste bag (see Screen 8.40).

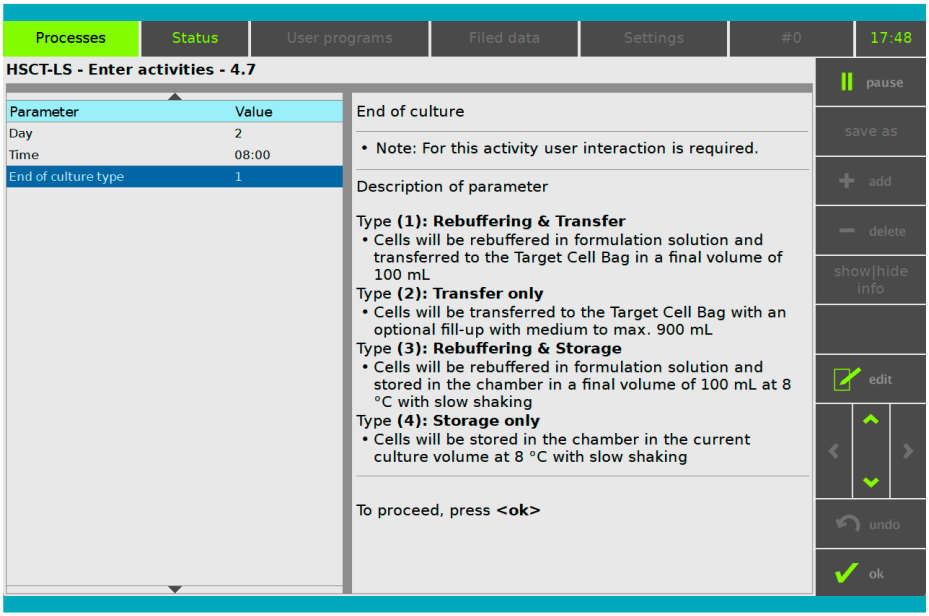
Read the barcode on the waste bag or tap <edit> to manually enter the information and tap <ok>. Confirm entered values with <ok> to complete the activity and return to the overview of the activity matrix.

8.5 End of culture

The harvest of the genetically-modified cells is executed by the final activity "End of culture".

The user can choose between 4 end of culture types (see Screen 8.41). The end of culture type must be programmed into the activity matrix during set up (see section 8.3 ´Setup of activity matrix´).

IMPORTANT
The standard processing time for HSCs is two to three days.



Screen 8.41: End of culture – Choice between four different end of culture types

End of culture type 1: Rebuffering & Transfer

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

End of culture type 2: Transfer only

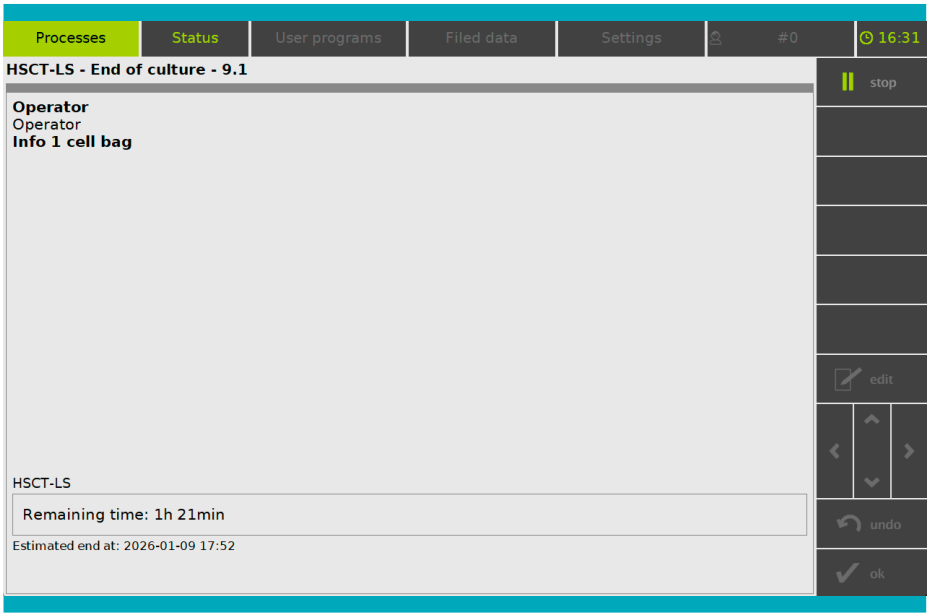
Cells will be directly transferred from the chamber to the Target Cell Bag. Optionally, the Target Cell Bag can be filled up with medium to an intended volume of up to 900 mL.

End of culture type 3: Rebuffering & 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.



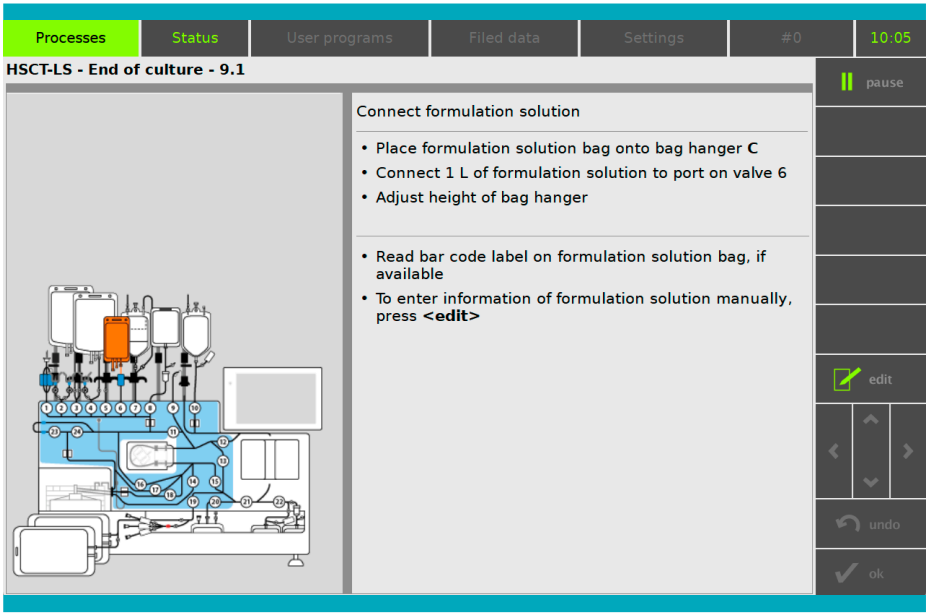
Screen 8.42: End of culture – Start Harvest

When the programmed time for "End of culture" is reached 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 activity "End of culture" is reached as temperature-monitoring and gassing is not maintained at this point.

8.5.1 End of culture type 1



Screen 8.43: Attachment of formulation solution

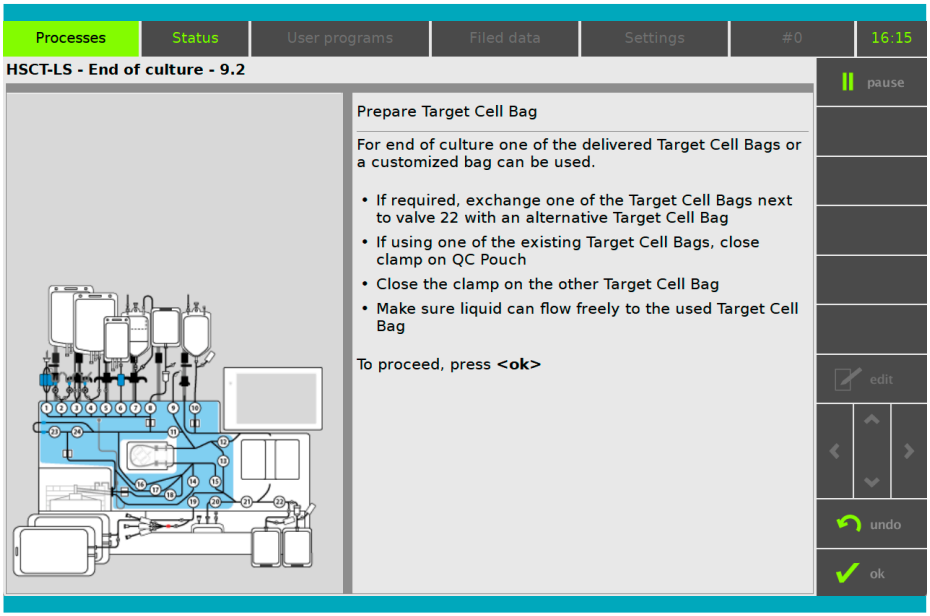
Prepare 1 L of formulation solution (for example sodium chloride solution for injection with 0.5% HSA) and follow the instructions on the <Processes> screen.

Connect the formulation solution to the spike port on valve 6 or via sterile welding below the filter (for example for CliniMACS Formulation Solution).

IMPORTANT
When a formulation solution with a protein content exceeding 0.5% is used (for example CliniMACS Formulation Solution), ensure to weld below the filter to remove it from the tubing set. Protein might cause clogging of the filter and impede sufficient fluid flow.

Read the barcode label on the formulation solution bag or tap <edit> to enter the information manually (see Screen 8.43).

Tap <ok> to continue.



Screen 8.44: Preparation of target cell bag on end of culture type 1

Cell filtration is an option when harvesting target cells. This is available with the pre-assembled in-line filter connected to one of the two designated Target Cell Bags. If using the in-line filter on the Target Cell Bag, make sure that the in-line filter is in an upright position.

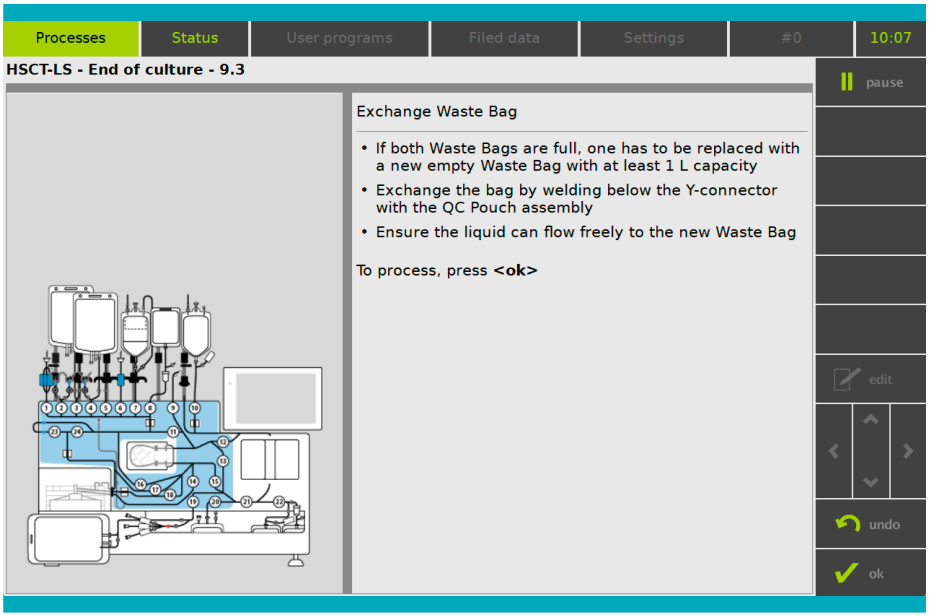
This can be achieved by replacing the separation column that has been sealed-off and removed from the magnet unit with the in-line filter to assure that the filter is hanging in an upright position during the transfer of cells into the Target Cell Bag.

If filtration of the cells is not required, choose the alternative Target Cell Bag. If another specific Target Cell Bag is required, sterile connect this Target Cell Bag between valve 22 and the in-line filter.

IMPORTANT

It is recommended to use the Target Cell Bag without the in-line filter for the HSCT-LS System. Using the Target Cell Bag with the in-line filter could result in a lower cell yield.

Close the clamps of the QC pouch attached to the Target Cell Bag and on the tubing path to the second Target Cell Bag not in use. Follow the instructions on the screen to prepare the Target Cell Bag (see Screen 8.44). The volume of the cell product will be 100 mL.



Screen 8.45: Exchange of waste bag

With the next screen the user is asked to exchange the Waste Bag. This is only necessary if the capacity of the current bag is nearly reached, and additional waste liquid capacity is required.

In this case, connect a new empty Waste Bag via sterile welding (see Screen 8.45).

Tap <ok> to continue. If an exchange of the Waste Bag is not required, tap <ok> directly. The automated rebuffering and harvesting step will take about 45 minutes. The cells in the chamber are washed twice with the formulation solution and are then transferred to the chosen Target Cell Bag on valve 22.

8.5.2 End of culture type 2

In the first screen the user is asked to exchange the Waste Bag. This is only necessary if the capacity of the current bag is nearly reached and additional waste liquid capacity is required (see Screen 8.45).

The End of culture Type 2 transfers the cell suspension to the Target Cell Bag. After the transfer, the chamber is rinsed twice with medium with cytokines. The volume in the Target Cell Bag will be the current culture volume before harvest plus 40 mL.

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

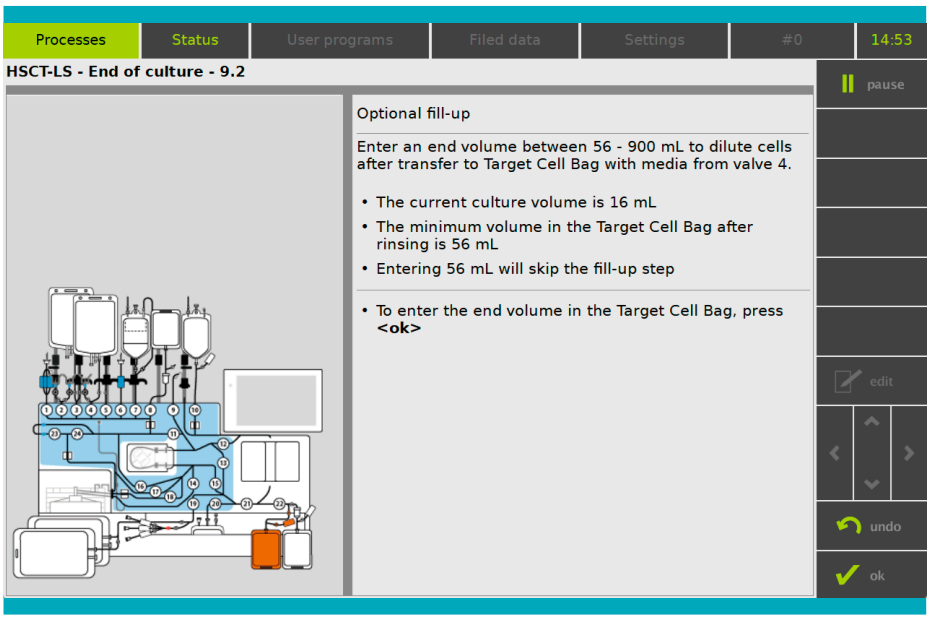
IMPORTANT

For volumes larger than 300 mL, the Target Cell Bag must be exchanged by a customized bag with sufficient volume capacity by sterile welding.

⚠ CAUTION

Risk of cell loss. The Target Cell Bag has a maximal capacity of 500 mL. If the Target Cell Bag is filled with more than 300 mL of cell suspension, mixing and handling of the bag after harvest can be unsafe.

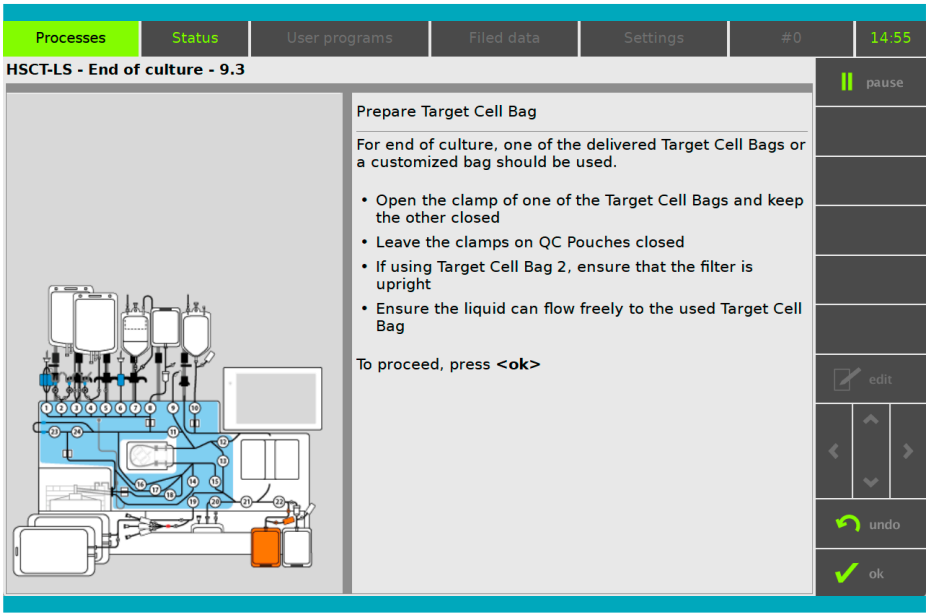
- Take this into account while programming the optional fill-up.



Screen 8.46: Optional medium fill-up during end of culture type 2

IMPORTANT

By setting the end volume to the current culture volume plus 40 mL (rinse volume), no additional fill-up will be performed (see Screen 8.46).



Screen 8.47: Preparation of Target Cell Bag or customized bag during end of culture type 2

8.5.3 End of culture type 3

In the first screen the user is asked to attach the formulation solution (see Screen 8.43).

In the second screen the user is asked to exchange the Waste Bag (see Screen 8.45). This is only necessary if the capacity of the current bag is nearly reached and additional waste liquid capacity is required.

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. If the cells are not kept under storage conditions as long as preparations for downstream processes are performed, the quality of cells can be lower.

- Keep the cells under storage conditions as long as preparations for downstream processes are performed.
- Proceed soon to ensure cell viability.

8.5.4 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

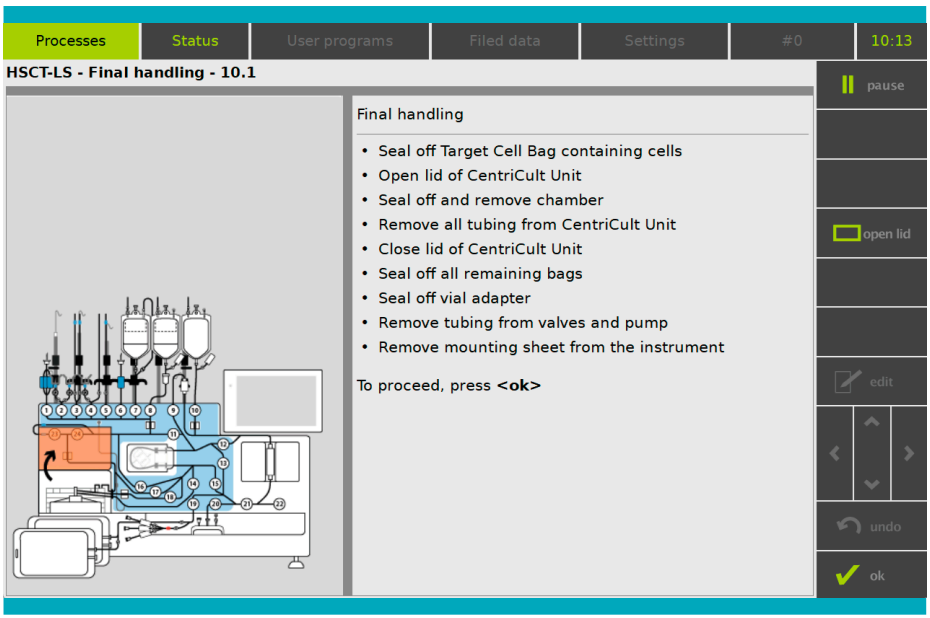
Risk of low performance. There is no time limit to stop the process when the cells are stored in the chamber. If the cells are not kept under storage conditions as long as preparations for downstream processes are performed, the quality of cells can be lower.

- Keep the cells under storage conditions as long as preparations for downstream processes are performed.
- Proceed soon to ensure cell viability.

8.6 Final handling

8.6.1 Final handling after end of culture type 1 and 2

After harvest of cells during the end of culture type 1 or 2, the program guides through the final handling steps.



Screen 8.48: Final handling

Seal off the Target Cell Bag containing the cell product. If required, take a sample from the Target Cell Bag for further analysis. The cells must be processed quickly after harvesting. Subsequently, follow all further instructions to remove the tubing set and to finalize the process.

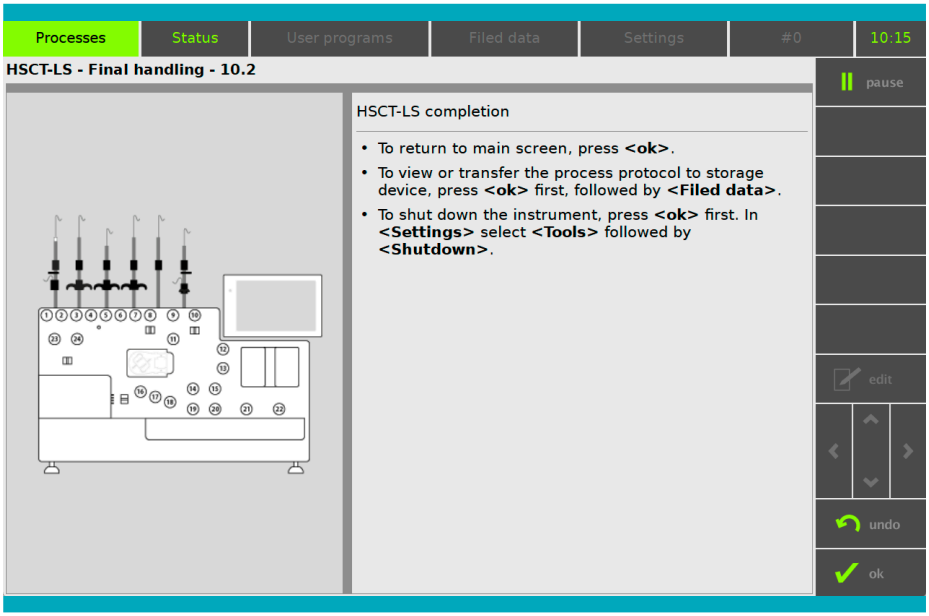
Follow the instructions given on the screen to remove the tubing set and to finalize the process (see Screen 8.48).

IMPORTANT

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.

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 8.49).



Screen 8.49: Process completion

The process protocol is stored in <Filed data> and can be transferred to other media by using a standard USB flash drive. To do so, plug a USB flash drive into the USB port located at the side of the monitor. Tap <Filed data> on the menu bar and select the requested process. Tap <save> to transfer the process protocol to the USB flash drive.

IMPORTANT

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

⚠ CAUTION

Risk of reduced quality of target cells. If the target cells do not meet user requirements, the suitability for clinical application can be compromised.

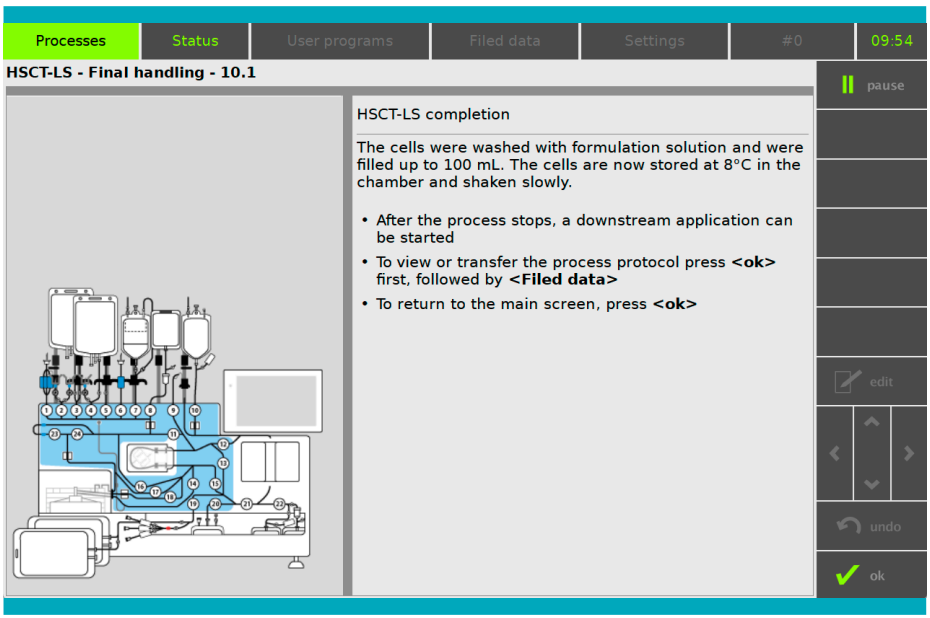
- Examine the target cells regarding quality and quantity according to their intended use.

All QC samples should be analyzed according to the standard operating procedures. For the manufacturing and use of the engineered HSCs, national and international legislation and regulations must be observed.

Miltenyi Biotec as the provider of the HSCT-LS process does not provide any recommendations regarding the use of the manufactured cells for therapeutic purposes and does not make any claim regarding a clinical benefit.

8.6.2 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 8.50: Process completion after end of culture type 3

Tap <ok> to stop the temperature control and shaking (see Screen 8.50). The CliniMACS Prodigy can then be used for a (customized) downstream process using the same CliniMACS TS 620.

The process protocol is stored in Filed data and can be transferred to other media with a standard USB flash drive. To do so, plug a 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. Tap <save> to transfer the process protocol to the USB flash drive.

The CliniMACS Prodigy must be cleaned and disinfected after each procedure. Refer to the CliniMACS Prodigy Instrument user manual regarding the cleaning and disinfection of the instrument. It is recommended to follow the institution's standard procedures for the treatment of infectious materials.

⚠ CAUTION

Risk of reduced quality of target cells. If the target cells do not meet user requirements, 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 manufacturing and use of the engineered HSCs, national and international legislation and regulations must be observed.

Miltenyi Biotec as the provider of the CliniMACS Prodigy Hematopoietic Stem Cell Transduction – Large Scale 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

10.1 Limited warranty

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

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

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

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

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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.

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210-005-784/01 | Issued: 2026-02