

Sefia™ expansion system

CELL THERAPY MANUFACTURING

Sefia™ expansion system (Fig 1) comprises three hardware components: process unit, media storage unit and status indicator as well as dedicated application software and dedicated single-use kits to provide a comprehensive solution to your cell therapy manufacturing process. This automated and functionally closed system covers cell activation, transduction and expansion resulting in a standardized process for reliable autologous cell therapy manufacturing (Fig 2).

- **Streamlined manufacturing.** Using the same system via a single procedure to cover three consecutive steps of your manufacturing workflow.
- **Flexibility to meet your process needs.** Customizable parameters and specific kits enable the system to adapt to your individual process; accommodating various reagents and media.
- **Designed to increase productivity.** Reduce operator touchpoints and labor hours with high level of automation over three consecutive steps to help optimize your resources and costs.
- **Features designed to reduce batch failure risks.** Functionally closed single-use kit helps keep contaminants out. Control your process with real-time lab dashboards and alert notifications.
- **Easy integration.** User-friendly design of applications and consumables. Centralized data traceability, consistent setup duplication and regulatory compliance thanks to Chronicle™ software connectivity.



Fig 1. Sefia expansion system including process unit, media storage unit and status indicator.



Fig 2. General workflow for cell therapy manufacturing. The Sefia expansion system enables to perform the steps highlighted in green.

System overview

Hardware

The Sefia expansion system has been designed to support cell culture over three key steps of the cell therapy manufacturing workflow. The liquid (reagents, cell product, solutions, sampling) and sterile air transfers are supported via 2 peristaltic pumps, 16 pinch valves and 4 electro valves. Loadcells on hooks in the media storage and tilting platforms assure mass measurement over the process. The two tilting platforms also support the mixing of the culture vessel when required. The incubation of cells with any reagents is possible with temperature and CO₂ control thanks to two bottom heating plates (one per tilting platform), one top heater, an incubation temperature sensor and liquid temperature sensors as well as CO₂ controller and sensor. Two fans are also here to ensure the homogenization of air inside of the process drawer. In addition two sensors allow the pressure to be checked for the kit test and enable failure detection during the process. Finally, the connectivity and the status of the equipment are provided by two LED indicators and an LED beacon, one ethernet port and nine USB ports.

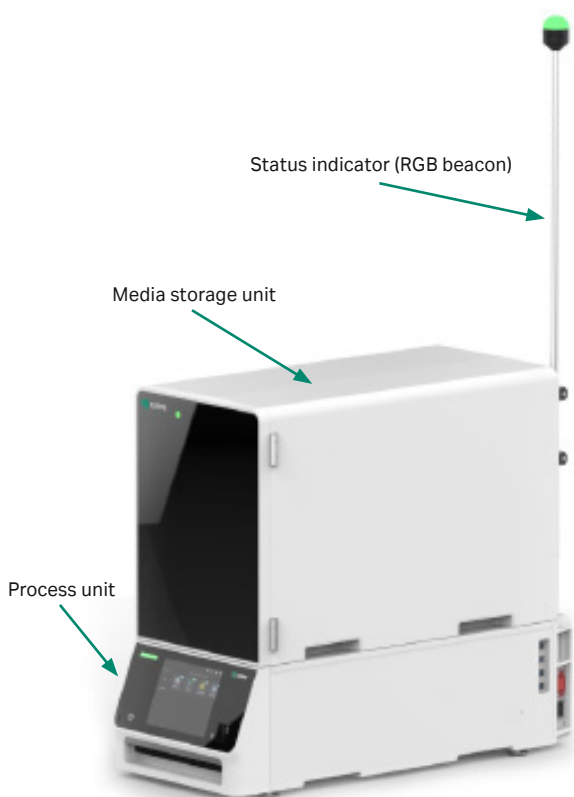


Fig 3a. Overview of Sefia expansion system components.

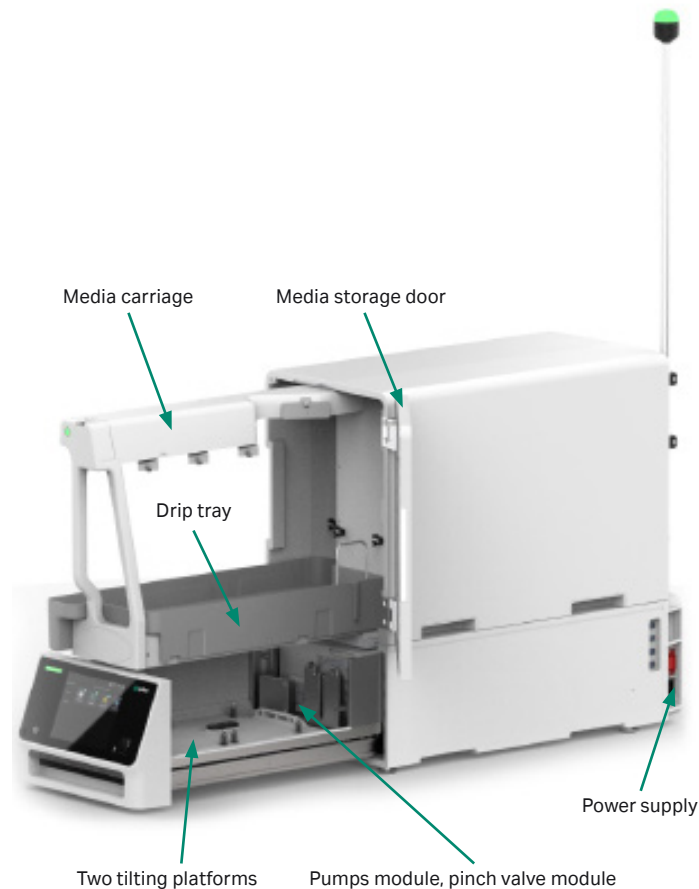


Fig 3b. Overview of Sefia expansion system components.

Software

All elements of the hardware are controlled by an embedded computer system with customized software for process automation accessed via a touchscreen user interface.

Universal application has been developed to cover the process steps required to activate the cell, transduce them with a viral vector, and finally expand cells to reach the target number.

Other applications have been developed to support additional needs such as troubleshooting.

| Applications | Step | Single-use kit | Product |
|------------------------|--|---------------------|---|
| Universal | Activation, transduction and expansion | Sefia expansion kit | Biological application allowing for flexible setup and execution of activation, transduction and expansion steps. |
| Purge | Troubleshooting | Sefia expansion kit | Troubleshooting application allowing to evacuate cells from the culture vessel in case of failure conditions. |
| Disengage | Utility | N/A | Usability application allowing to disengage kit engagement mechanism outside of the biological application execution. |
| Diagnostic tool | Diagnostic | N/A | Application that allows user to automatically assess functionality of critical parts of the instrument. Application provides complete pass/fail report. |

The Sefia expansion system can be connected to Chronicle automation software to monitor cell therapy manufacturing operation and supply chain logistics. Chronicle software enables the digitization of manufacturing documentation by generating electronic batch manufacturing records (eBMRs) through the use of electronic standard operating procedures (eSOPS). It also offers the ability to monitor instrument data in real-time and receive alert notifications via SMS and emails. Chronicle software centralizes the creation, approval, and deployment of parameter groups on connected Sefia expansion systems. Chronicle software supports cell therapy process development and manufacturing in compliance with FDA 21 CFR part 11 and EU Annex 11.

Consumables

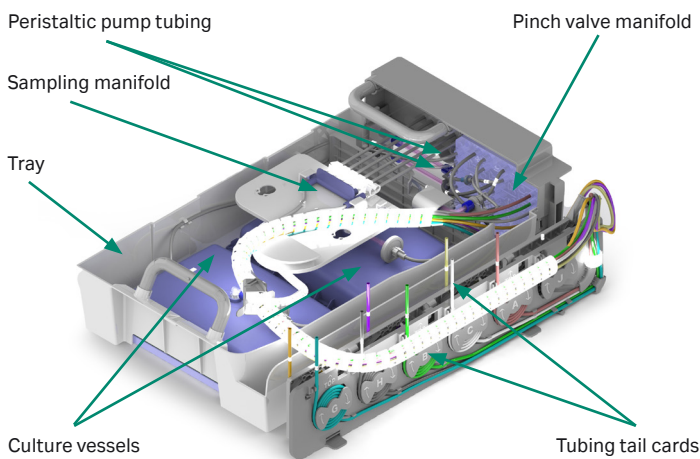


Fig 4. Sefia expansion single-use kit.

The Sefia expansion kit is a single-use kit for activation, transduction and expansion during CAR T cell therapy manufacturing processes. The kit is functionally closed, sterilized and contains two culture vessels as well as an array of tubing (Fig 4). The media and reagent lines of the kit are fitted to two tubing tail cards. The lines are color-coded to ease identification. The working mass of liquid is up to 628 g per vessel.

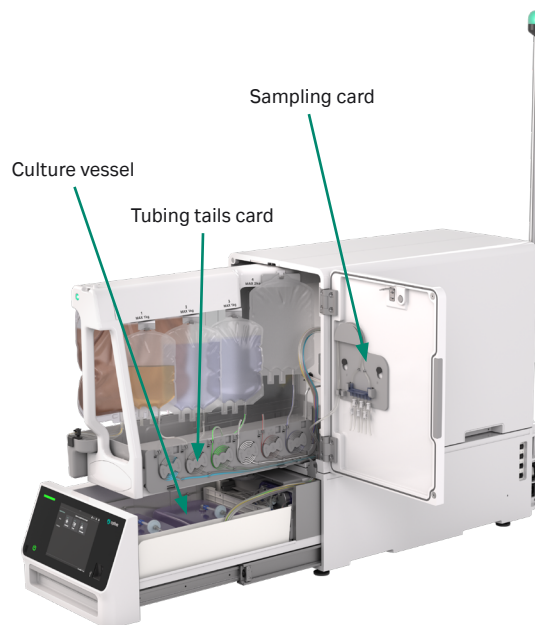


Fig 5. Sefia expansion kit installed on Sefia expansion system.

In addition, each Sefia expansion kit is equipped with an attached sample card (Fig 5). The sample card holds the sample manifold and six sample tails for collecting samples during a run. All sample tails are equivalent, and their use should be managed by the user.

Sefia expansion kit is available in two types (FEP: fluorinated ethylene propylene and Si: silicone) to meet different customer needs. They both have the same volumes, the same architecture and are compatible with Universal application. The difference is the membrane material used for the culture vessels. In one of the kits, the membranes are FEP and in the other kit, they are silicone (Fig 6).

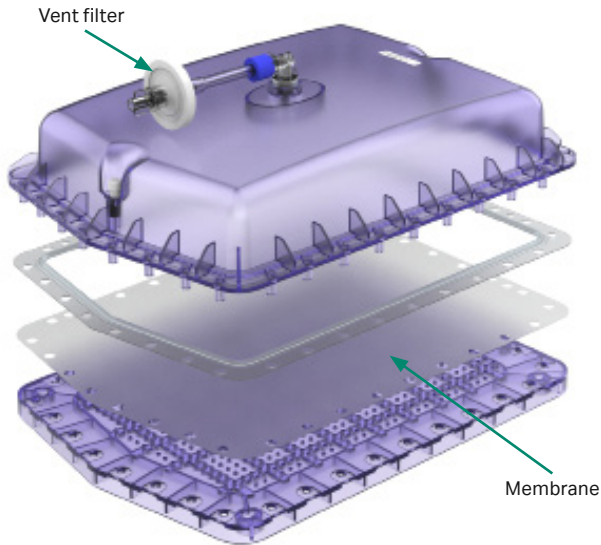


Fig 6. Detailed view of culture vessels including membrane and vent filter.

The vent filter is used during the kit test for pressure monitoring inside of the culture vessel and during the process for venting culture vessel to prevent excess pressure.

The membrane allows gas exchange between the culture and the external environment.

The four sterile air filters of each kit and the sterile air filter of the waste bag are integrity testable to help customers meet regulatory requirements. The test enables demonstration of the sterility of the filter and confirms that the filter has not been compromised during the procedure.

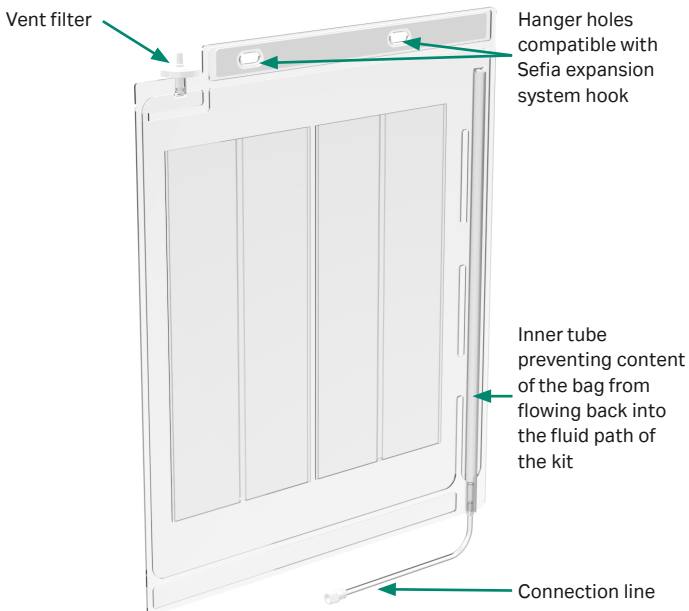


Fig 7. Sefia expansion waste bag.

The waste bag (Fig 7) is available as a standalone consumable of the Sefia expansion kit to be able to connect as many waste bags as required during your specific process. It is recommended to use Sefia expansion waste bag when using Sefia expansion system.

Universal application overview

The Universal application covers three consecutive steps of your cell therapy manufacturing process: cell activation, transduction and expansion. You can start a procedure with Universal application with cellular product using a mass of between 5 and 250 g. Universal application default parameters are designed to execute one of many possible types of workflow, typically taking between 5 to 12 days. The cells are cultured in static culture vessels with temperature and CO₂ concentration control and monitoring. Sefia expansion system can be used with your current reagents and media. It has been tested with market-leading activators and media as well as various types of viral vectors. Different methods can be used to support the cell expansion: batch, fed-batch or perfusion (Fig 8). At the end of the procedure, the genetically modified and expanded cells will be harvested in a bag up to 1200 g.

Key features of Universal application

| | |
|--|---|
| Initial cellular product mass | 5 to 250 g |
| Harvest bag | Up to 1200 g |
| Typical processing duration ⁽¹⁾ | 5 to 12 days |
| Supported expansion method | Batch Fed-batch Perfusion |
| Type of culture | Static |
| Control and monitoring | Temperature and CO ₂ concentration |

⁽¹⁾ For default parameters, may vary based on initial seeding cell number, used reagents and type of membrane used.

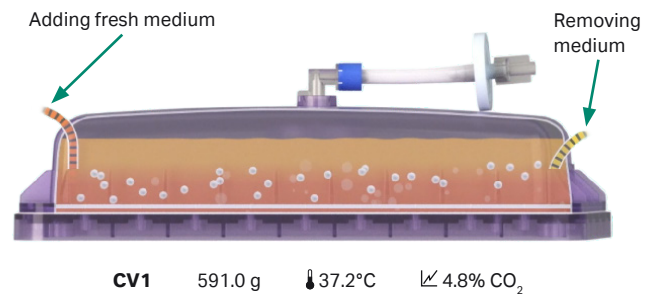


Fig 8. Illustration of cell expansion with perfusion method in Sefia expansion culture vessel (CV).

Sefia expansion system Universal application offers high flexibility with customizable parameters that allow the operators to optimize activation, transduction and expansion steps. For example, you can perform in parallel some activation steps and some transduction steps to optimize processing time (Fig 9).

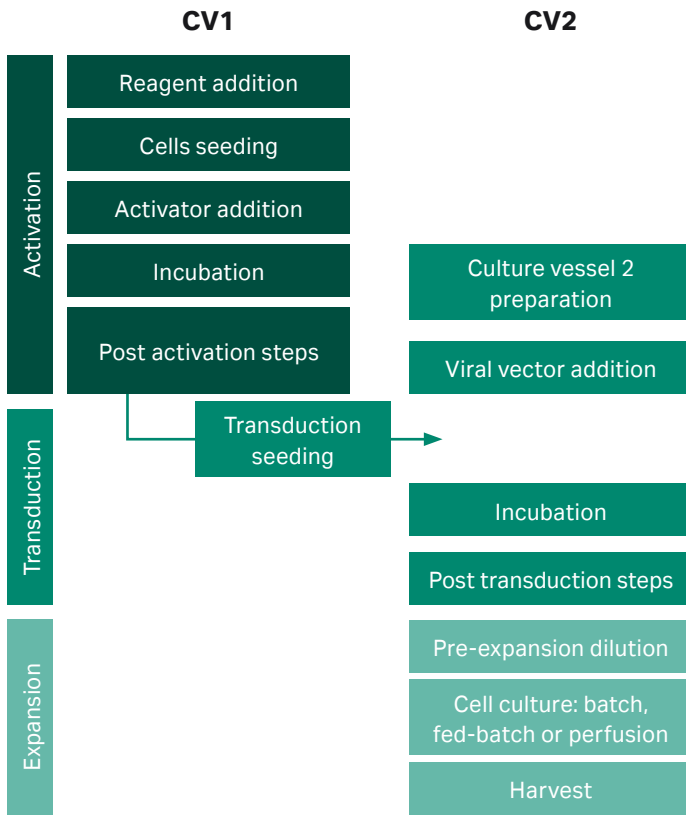


Fig 9. Example of workflow with parallel activation and transduction steps to optimize processing time.

You can also use the two culture vessels (CV) for the cell expansion by moving a portion of the cells from CV 1 to CV 2 and perform a parallel expansion step to optimize the final cell number (Fig 10).

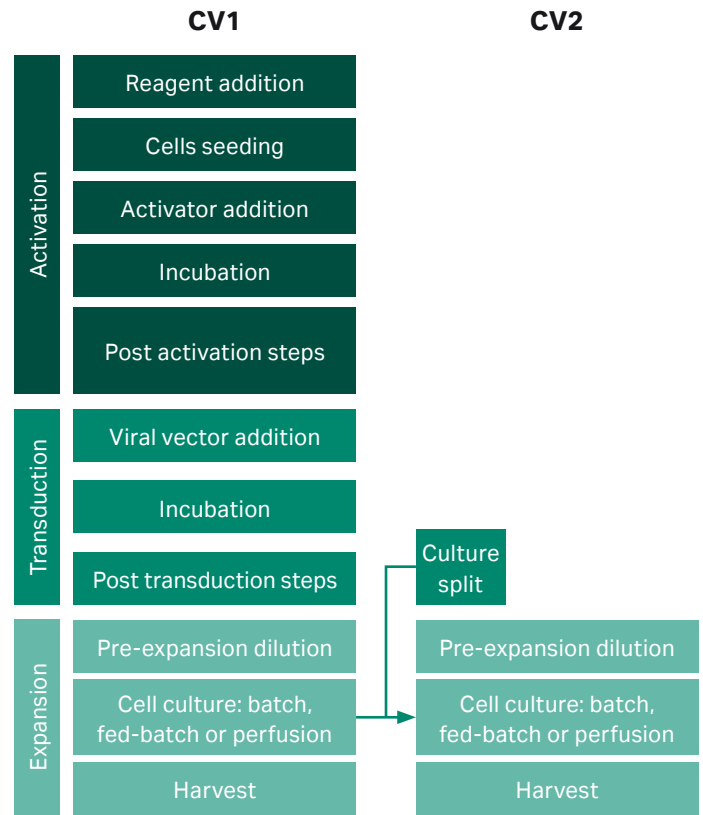


Fig 10. Example of workflow with parallel expansion step to optimize final cell number.

Performances

In the table below, of the performances obtained with the Sefia expansion system transduction efficiency at harvest over six experiments, three have been generated from fresh healthy donor apheresis and three from frozen healthy donor apheresis. Each apheresis has been processed using MagnetSelect application on Sefia Select system to isolated the T-cells. Then the isolated T-cells have been used as starting materials

on Sefia expansion system to start the Universal procedure covering activation, transduction and cell expansion.

These performances are given for information as performance depends on parameter setting, used reagents and media as well as initial cellular product. The workflow can also be used for other types of viruses, activators and cell culture media.

| Step | Description | Fresh healthy donor (n=3) | Frozen healthy donor (n=3) |
|-------------------|---|---|---|
| Activation | Initial cellular product | Isolated T-cells from apheresis | Isolated T-cells from apheresis |
| | Activator | T Cell TransAct | T Cell TransAct |
| | Total viable cell seeding number for activation | 100 × 10 ⁶ in 150 mL suspension | 100 × 10 ⁶ in 150 mL suspension |
| | Activation marker expression post-activation | 99.3% | 84.2% |
| | Cell viability post-activation (day 5) | 96.7% | 95.2% |
| Transduction | Transduction efficiency at harvest | 58.3% | 52.2% |
| | Cell viability post-transduction | 96.7% | 95.2% |
| Expansion/general | Cell culture medium | Akron ImmunoCell Growth Medium (serum free) | Akron ImmunoCell Growth Medium (serum free) |
| | Average daily fold expansion | 2.26 | 1.84 |
| | Cell viability at harvest | 98.1% | 96.3% |
| | Cell recovery of cells from the culture vessel at time of harvest | 96.0% | 94.8% |
| | Number of cells at the end of the workflow | 4.9 × 10 ⁹ T-cells (day 8) | 2.55 × 10 ⁹ T cells (day 9) |

Specifications

Hardware

| Feature | Sefia expansion system |
|----------------------------|--|
| Dimensions (W × L × H) mm | System with RGB beacon: 380 × 886 × 1477 (adjustable to ± 150) System without RGB beacon: 380 × 886 × 768 |
| Weight | Process unit: 42.2 kg Media storage unit: 38.8 kg |
| Power consumption | 1000 W |
| Input voltage | 100 to 240 VAC |
| Frequency | 50/60 Hz |
| Core technology | Two tilting platforms 2 peristaltic pumps, 16 pinch valves and 4 electro valves Two pressure sensors Temperature and gas control Weight sensors on each hook and each tilting platform Culture volume range from 125 g to 1.2 kg (up to 628 g per vessel) |
| CO ₂ connection | PMC 1603-3/16 hose barbed, non-valved connector Minimum: 1.2 bar and maximum: 5 bar 288 L/day as maximum CO ₂ consumption/leak rate |
| Connectivity | One ethernet port and nine USB ports |
| Software | Compatible with Sefia expansion applications only, Windows 10 and proprietary Sefia expansion software |
| User interface | Color touchscreen with an intuitive graphical user interface (GUI) Dynamic user guide to support operations |
| Traceability | Data management with PDF reports |
| User authentication | Role based configuration Authentication and permission using a customer's ActiveDirectory (AD) server |
| Electronic signature | Electronic signature is performed in Chronicle automation software only |
| Data exchange | Encrypted and secured |
| System log/audit trail | Every system action is recorded in the system log Data transfer populates associated equipment logs in Chronicle automation software |

Consumables

| Feature | Sefia expansion kits and waste bags |
|---|---|
| Shelf life | The kits and waste bags have a shelf life of two years when stored at recommended storage temperature. |
| Sterility | Sterile by gamma irradiation, for kits and by ethylene oxide for waste bags refer to the related validation guide for more information. |
| Materials in contact with cellular products | Polycarbonate (PC), fluorinated ethylene propylene (FEP), polypropylene (PP), polyvinyl chloride (PVC), silicone, and methylmethacrylate acrylonitrile butadiene styrene (MABS). |
| Lines | All the single-use kit line tails handled by the user as well as waste bag lines are compatible with sterile connection (SCD). Outer diameter (OD) is 4.1 mm and inner diameter (ID) is 2.6 mm for the weldable lines (PVC). |

Safety and compliance

Sefia expansion system, combining a process unit and media storage unit, is a laboratory instrument with the CE mark (Machinery Directive 2006/42/EC). The system is intended for cell therapy manufacturing in good automated manufacturing practice (GAMP) compliant environments. The system is compliant with IEC-61010, IEC-61326, ICES-001 EMC requirement for Canada (Class A) and, China RoHS SJ/T11364-2014 standards.

Chronicle enables technical compatibility with ISPE GAMP 5, FDA 21 CFR Part 11 and EU GMP Annex 11 compliance.

Storage and operating requirements

Hardware

In addition to the environmental requirements outlined in the following table, installation of the Sefia expansion system must comply with the following general requirements:

- The room must have exhaust ventilation.
- The room must have forced ventilation for use of CO₂.
- The instrument should not be exposed to sources of heat, such as direct sunlight.
- Dust in the atmosphere should be kept to a minimum.
- The equipment must not be exposed to vibrations.

| Parameter | Requirement |
|--|----------------------------|
| Allowed location | Indoor use only |
| Altitude, operating | Up to 2000 m |
| Ambient temperature, operating | 15°C to 25°C |
| Ambient temperature, storage | 0°C to 50°C |
| Atmospheric pressure, operating | 840 to 1060 mbar |
| Pollution degree of the intended environment | Pollution degree 2 |
| Relative humidity, operating | 20% to 80%, non-condensing |
| Relative humidity, non-operating | 20% to 80%, non-condensing |

Consumables

The table below highlights the environmental requirements for storage and transport of Sefia expansion. Sefia expansion kits and waste bags must be stored in a clean and dry environment without chemical or biological contamination.

| Mode | Storage |
|-------------|----------------|
| Temperature | +10°C to +30°C |

Service information

OptiRun™ service solutions

Regulatory authorities require systems to be qualified and maintained within specifications during use in process scale-up and GMP-manufacturing. Our OptiRun™ service solutions offer a comprehensive range of services throughout the product's life cycle to support your technology, processes, and people.

| Services | Product |
|--|---|
| Equipment installation | Installation can be performed by trained Cytiva service engineers |
| Preventive maintenance | Replacement of wear-and-tear parts and functional testing to ensure continuous performance of your instrument |
| Installation/operational qualification (IQ/OQ) and re-qualification (RQ) | Standard and custom qualification services for Cytiva equipment throughout its life cycle, including IQ/OQ, RQ, and continuous verification |
| Instrument upgrades | Hardware and software upgrades to keep your equipment state-of-the-art during its life cycle |
| Repairs | Field, remote and mail-in repairs are available depending on your instrument type and environment |
| Digital services | A range of digital solutions, from remote assistance to network installation and virtual support and trainings |
| Spare parts | High quality spare parts for use in GxP environment; parts security of supply consultancy |
| Relocation support | Preparing your equipment to be moved and re-installed in its new location |
| Service plans | A range of plans to support your operations and instrument performance |

Ordering information

| Products | Product code |
|--|--------------|
| Sefia expansion system package (including process unit, media storage unit and status indicator) | 29746257 |
| Sefia expansion media storage unit | 29722941 |
| Sefia expansion system (process unit) | 29413640 |
| Sefia expansion status indicator (RGB Beacon) | 29722942 |
| Sefia expansion kit - FEP/FEP | 29716713 |
| Sefia expansion kit - Si/Si | 29739346 |
| Sefia expansion waste bag (10 pack) | 29732203 |

| Related products | Product code |
|---|--------------|
| Chronicle software Pre-GMP base annual subscription | 29734890 |
| Chronicle software GMP base annual subscription | 29734894 |
| eBinder IQ/OQ Sefia expansion system | 29745977 |

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While the Sefia expansion system is a leading cell therapy solution with broad capabilities, Cytiva has not validated and verified all workflows or use cases.

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