CELL THERAPY SOLUTIONS

Extract Technology, Cell Therapy Isolator.
4Medical Innovations Biomedical Park
Ostrava, Czech Republic

Innovation to protect

Since 2013 the Finnish Red Cross have been using Extract Technology's Cell Therapy Isolators primarily to produce allogeneic mesenchymal stromal/stem cells for the treatment of hematopoietic stem cell transplant patients.
(Salmenniemi et al. 2017; Keto et al. 2018).

www.bloodservice.Ï

Typically, stem cells are developed for 21-30 days before being reintroduce as an individual patient therapy.

Among the processes undertaken are long-term cell culture cultivation in cGMP (adherent and suspension cells) including mesenchymal stromal cells and T-cells. Additionally, they provide graft engineering services such as advanced cell selections to enable haploidentical stem cell transplantations.

Rapid cell isolations, both open and closed processing.

- Optimization of cell culture conditions
- Xenofree culture conditions and supplements (blood-derived supplements)
- Cell characterization and functional studies
- QC assays
- Stability studies

Mesenchymal stromal cells (since 2013)

- >70 patients

Autologous keratinocytes (2014-2018)

- 20 patients (36 products)

} **ATMPs**
Hospital Exemption
National ATMP Production Permit

Hematopoietic stem cell transplant processing service (since 2017)

- TCRα/β-CD19 depleted stem cell transplants
- CD34 enriched stem cell transplant

} **Tissue products**

Process Development and Research:

- NK Cell therapy product for clinical use (Professor. Kim Vettenranta)
- CAR-T cells (Adjunct Professor. Matti Korhonen) Source: Anita Laitinen, Finnish Red Cross

Information compliments of Johanna Nystedt, Director of Supervision and Licenses, Finnish Red Cross.

Finnish Red Cross

Finnish Red Cross Advanced Cell Therapy Center (ACTC), Helsinki University Hospital.

CELL THERAPY CLINICAL TRIALS

2017

946

Clinical tirals underway worldwide by end of 2017

Ph. I: 314
Ph. II: 550
Ph. III: 82

Number of Clinical Trials Utilizing Specific RM/AT Technology: 2017

Gene Therapy

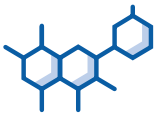
Total: 313
Ph. I: 113
Ph. II: 170
Ph. III: 30

Gene-Modified Cell Therapy

Total: 259
Ph. I: 106
Ph. II: 144
Ph. III: 9

Cell Therapy

Total: 353
Ph. I: 90
Ph. II: 225
Ph. III: 38



Tissue Engineering

Total: 21
Ph. I: 5
Ph. II: 11
Ph. III: 5

2018

1,028

Clinical tirals underway worldwide by end of 2018

Ph. I: 341
Ph. II: 595
Ph. III: 92

Number of Clinical Trials Utilizing Specific RM/AT Technology: 2018

Gene Therapy

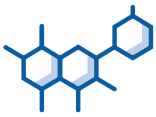
Total: 362
Ph. I: 120
Ph. II: 210
Ph. III: 32

Gene-Modified Cell Therapy

Total: 362
Ph. I: 158
Ph. II: 188
Ph. III: 16

Cell Therapy

Total: 364
Ph. I: 53
Ph. II: 177
Ph. III: 33



Tissue Engineering

Total: 341
Ph. I: 10
Ph. II: 20
Ph. III: 11

All data courtesy of ARM - Alliance for Regenerative Medicines

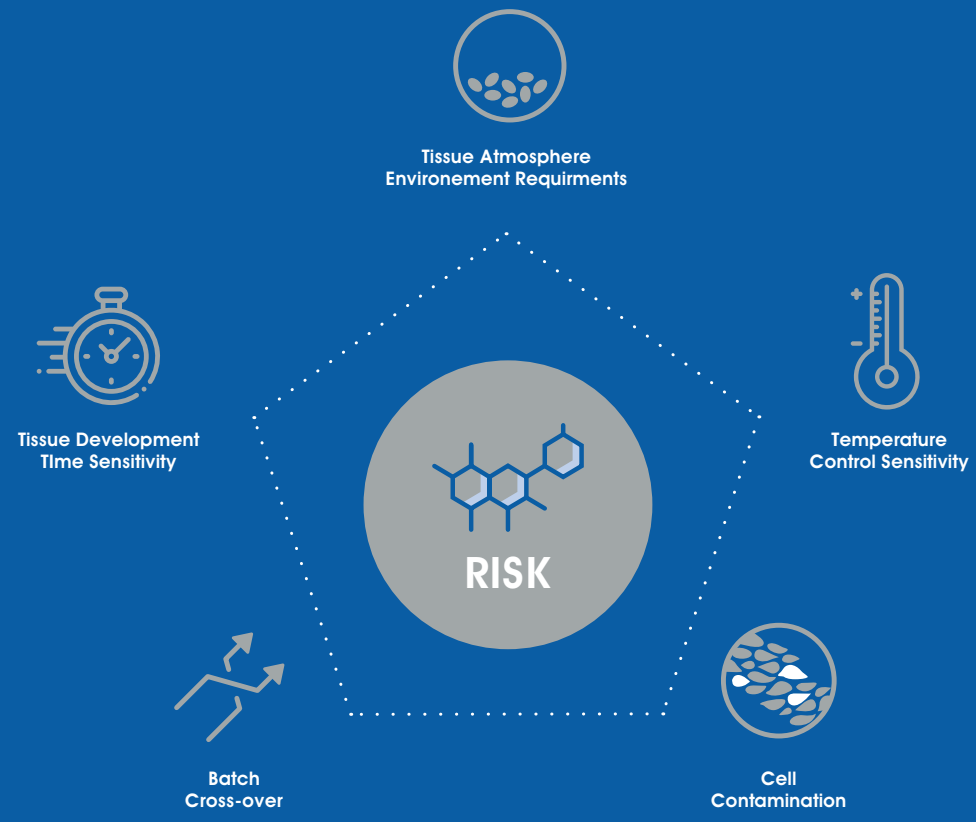
Alliance for Regenerative Medicine

TISSUE ENGINEERING

Tissue-engineering applications are extremely wide ranging. Spanning both hard and soft tissue from bone and marrow to the generation of organ and vascular tissues. Like other ATMPs, the tissue-engineering production process is impacted by a number of risks.

CELL THERAPY PRODUCTION RISKS

The challenge for manufacturers aiming to ensure patient safety at the lowest possible cost lies in specifying facilities to cGMP draft guidelines whilst getting to market quickly. Compromising on production process and facility assets is more costly than the upfront investment. Reduced batch contamination and faster delivery to market results in saved lives.



FACILITY DESIGN FLEXIBILITY

Advancements in 4.0 pharma are driving the need for facility design solutions to deliver cost savings.

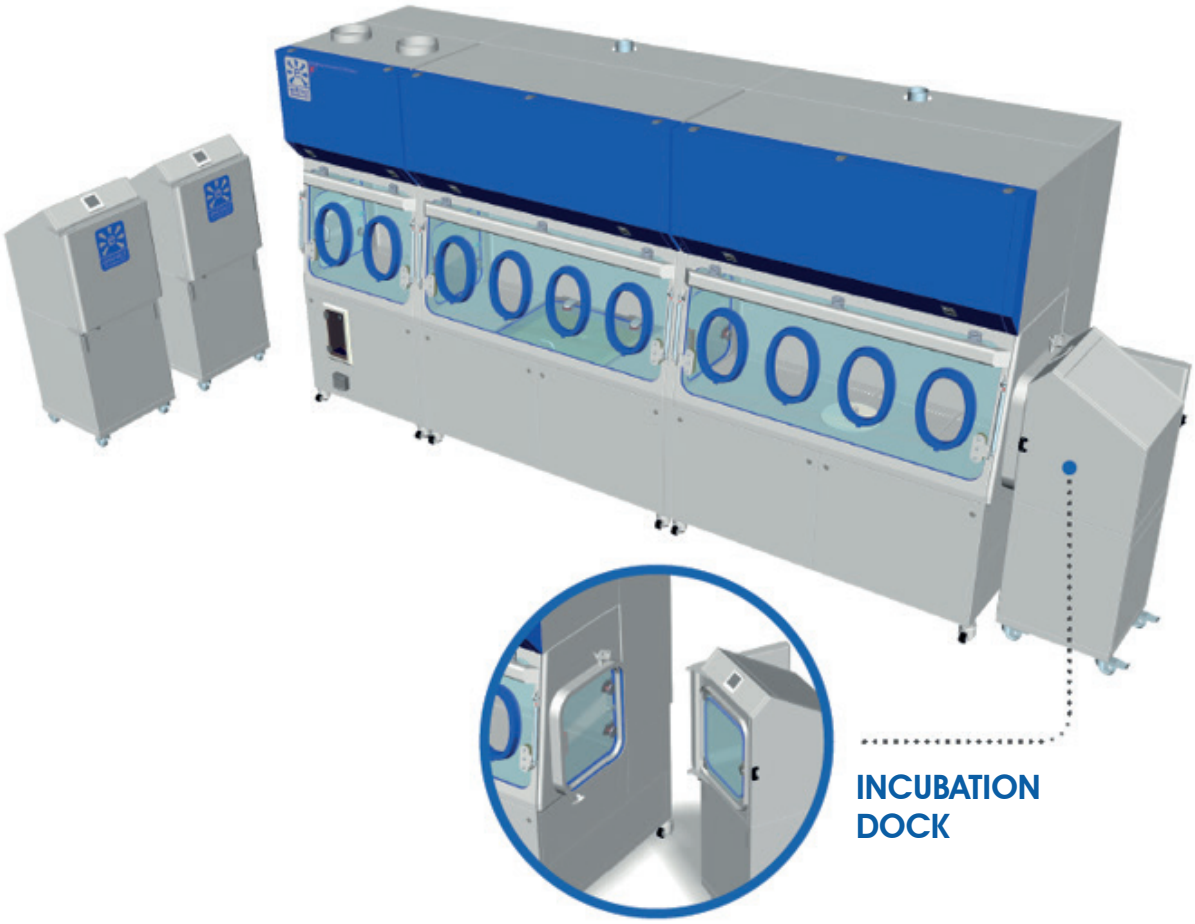
Cell and gene therapies are currently produced in facilities that require signiÏcant upfront investment and high per patient cost. The future of facility design is leaning on pillars including automation and innovation to reshape the way we use Ïxed assets and the production process as a whole.

Integration of closed processes such as isolators into the largely human workÌow is an increasingly effective method to adopt production eÏciency that improves patient safety and reduces contamination along with overall costs.

Modern offerings such as modular concepts provide an opportunity to shift from larger, Ïxed assets or open environments to networks of smaller processing systems.

Multiple chambers allows Ìexibility to integrate customized equipment. State-of-the-art isolator technology provides a closed aseptic environment with automated functionality to maintain a safe, controlled environment for cell production. This has the added beneÏt of reducing HVAC costs and the need for excessive gowning and sterilization of large cleanroom spaces.

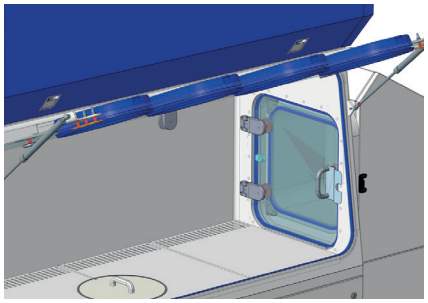
PLC control systems with HMI interfaces are a standard feature. Modules can be joined to accommodate processing needs so companies can scale their facility and production incrementally. Standardization of manufacturing systems allows producers to accelerate delivery of therapies to market while increasing product quality and patient safety.

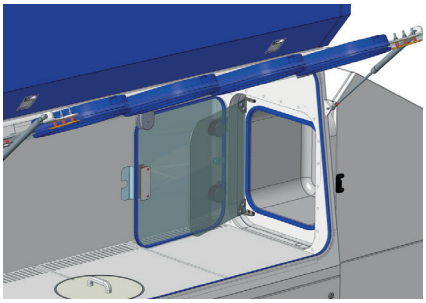


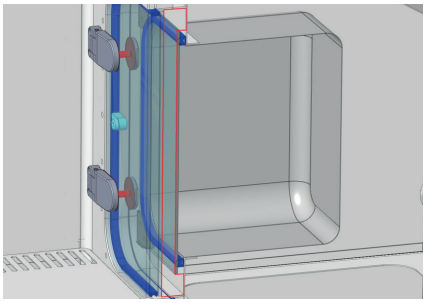
Extract Technology's patent pending Cell Therapy Isolator can be used in a variety of cell and gene therapy environments.

Unlimited incubator pods can be arranged to support a flexible number of cells. Incubator pods are stored at the docking station when not in use and moved to the isolator when required.

Dockable incubators enable an increase in working area allowing multiple cell cultures to be treated separately.







REGULATIONS AND CURRENT GUIDES

ATMPs manufactured within an aseptic environment must be carried out under Grade A ISO 4.8 airflow to EU cGMP Annex 1, ISO 14644-1 and is regulated by the US Center for Biologics Evaluation and Research (CBER) under the FDA.

Modular closed systems allow a Grade A Cell Therapy Isolator to be positioned in a lower grade environment as opposed to LAF cabinet in Grade B environment.

For example Grade D/ISO8 cleanroom with a Grade A/ISO4.8 isolator eliminates the need for graded step increases and additional gowning and validation, saving time and money.

BENEFITS

01. cGMP design provides product assurance and regulatory compliance enabling rapid delivery to patient
02. Full process equipment integration within Grade A / ISO 4.8 environment
03. HVAC costs reduced with a closed system isolator vs LAF cabinet in Grade B environment
04. Decrease validation including time and costs of filter integrity testing
05. Decrease cleaning validation
06. Decrease gowning and training
07. Increase in staff retention
08. Decrease human intervention resulting in reduced risk of batch cross-over
09. Reduce risk of contamination by using barrier technology
10. No direct contact between technician and cell culture increases patient safety
11. Multiple and dedicated chamber arrangements allow for process separation and material flow control
12. Integrated vapor phase hydrogen peroxide (VPHP) decontamination
13. Smaller operational space results in reduced decontamination time
14. Automated environmental controls with all measurement data transmitted to DMS for data integrity
15. Ergonomic design generated by the use of sloping front face, large oval PharmaPort gloveports
16. Process efficiency improvements allow reduction in per patient cost making manufacturers more resilient and treatment accessibility to patient population

HOW DOES IT WORK?

As part of the standardized product range, the Modular Cell Therapy Isolator is a cost-effective alternative solution for the safe processing of cells.

Available in a basic conïguration but with a wide range of optional integrated equipment. It can be increased in both size and ìexibility to satisfy speciïc process requirements.

Grade A/ISO 4.8 temperature controlled and bio-decontaminated chambers make processing cells safe for patients and easy for technicians.

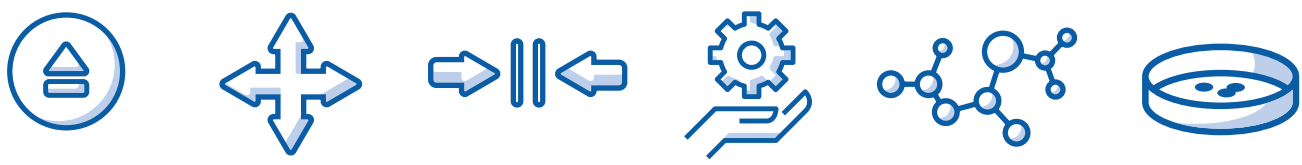
Each chamber is positively pressurized relative to the room and the ante-chambers to ensure no viable particles are transferred into the aseptic chamber following decontamination.

Both viable and non-viable particle counting methods are employed close to the process in order to continually monitor the environment conditions ensuring repeatability in all steps. Before work can start, each chamber is bio-decontaminated using VPHP (vapor-phase hydrogen peroxide) utilizing an integrated gas generator.

EASE OF USE

Extract technology has been designing and manufacturing isolators for decades. Leaning on 50 years of experience in the pharmaceutical industry in the design of Modular Cell Therapy Isolators to provide the most cost-effective and easy to use solution.

UNDOCK MODULAR STATION — **TRANSPORT** — **CONNECT AND DECONTAMINATE** — **RETRIEVE MATERIAL** — **PROCESS CELL CULTURES** — **RETURN TO INCUBATOR**



DECONTAMINATION

The onboard Vapor Phase Hydrogen Peroxide rapid gassing system enables operators to handle cellular products in a highly controlled process flow.

The bio-decontamination ensures a 6-Log reduction in bacterial spore population with integrated safety features to guarantee operator and plant safety. Increased protection from contamination is achieved by reducing human interventions, physical barrier technology, pressure differential and routine VPHP.

Hydrogen peroxide (H_2O_2) is recognized by the FDA and other regulatory agencies as an effective method of surface bio-decontamination.

Full H_2O_2 high/low level monitoring is integrated into the control system. An external H_2O_2 sensor is incorporated for room monitoring. H14 Grade HEPA ïlters are provided, as a minimum, on all isolators designed and manufactured by Extract Technology.

BIO-DECONTAMINATION

6-Log

Reduction in spore population

AIR CLASSIFICATION

ISO 4.8 Grade A

Unidirectional airflow

CONFIGURATION

In order to suit the requirements of your process, a variety of modules can be placed in sequence.

Process equipment can be integrated to accommodate unique application needs and modules can be added as your business grows.

Our Engineering team will work with you for conïguration to your process application needs around the standard modular structure.

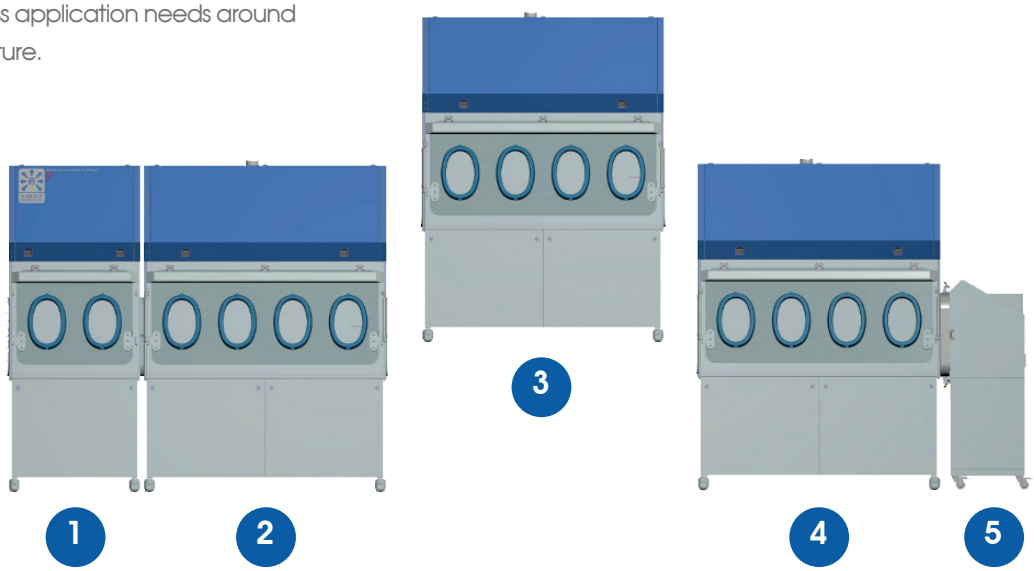
01. Transfer Chamber

02. Centrifuge Chamber

03. **New Process Chamber**

04. Process Chamber

05. Incubator Pod



ALTERNATIVE CONFIGURATION

INTEGRATED EQUIPMENT OPTIONS

A variety of equipment can be integrated within the isolator chamber to satisfy the requirements of your process.

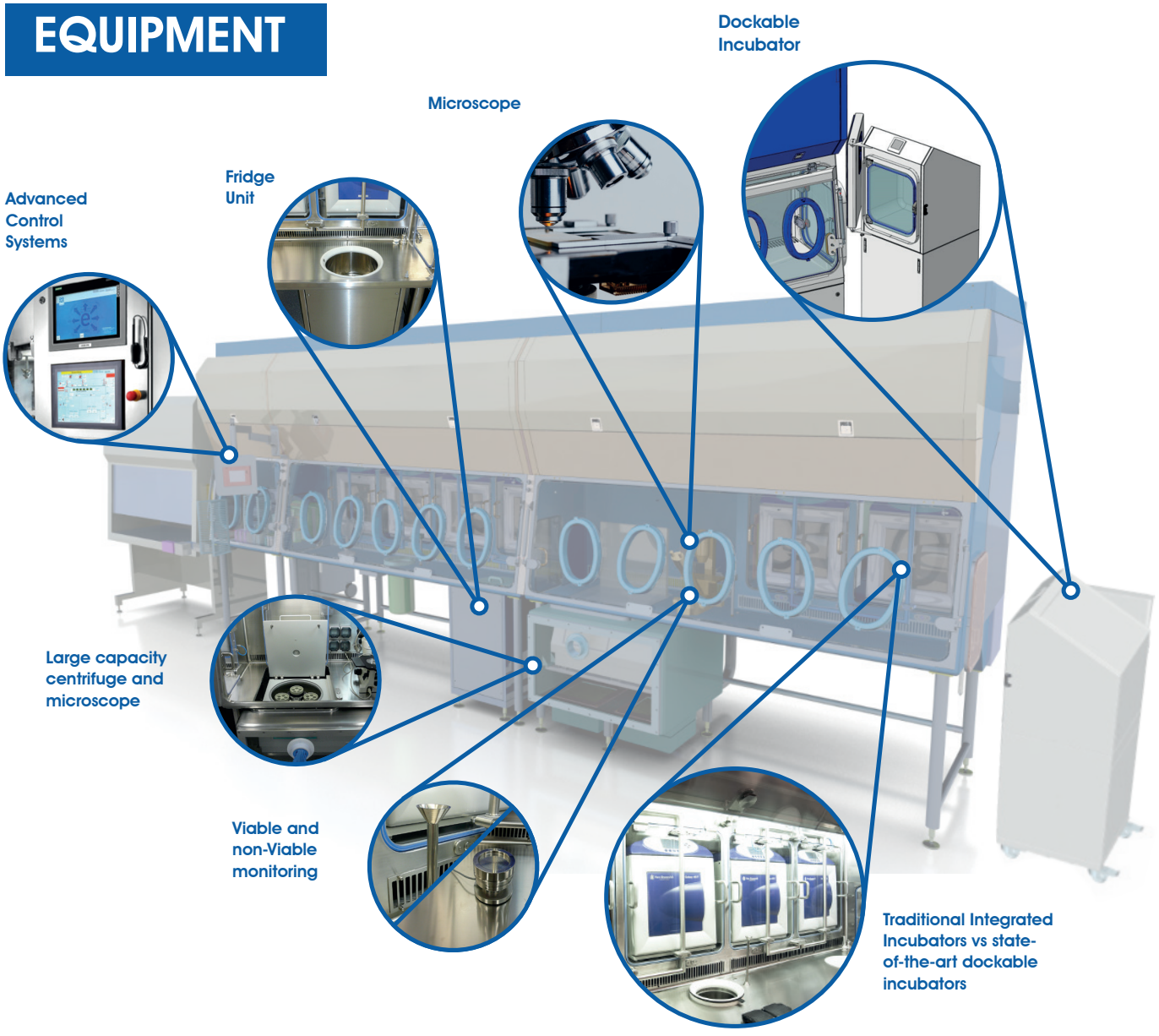
- Transfer hatch
- LAF cabinet for cell introduction
- Integrated fridges
- Centrifuge chamber
- Viable or non-viable particle monitoring
- Microscopes
- Small-scale lab benchtop equipment such as stirrers and shakers
- Additional at request

STANDARD DIMENSIONS
CELL THERAPY ISOLATORS

	CHAMBER HEIGHT mm (inches)	CHAMBER DEPTH mm (inches)	CHAMBER WIDTH mm (inches)	CTI OVERALL HEIGHT	CTI OVERALL DEPTH	CTI OVERALL WIDTH
CONTROL TOWER	2530 (99-1/2")	1230 (48-1/2")	400 (15-3/4")	2530 (99-1/2"	1230 (48-1/2")	5100 (200-3/4")
AIRLOCK / TRANSFER	850 (33-1/2")	730 (28-3/4)	1000 (39-1/2")			
CENTRIFUGE CHAMBER	850 (33-1/2")	730 (28-3/4)	1840 (72-1/2")			
PROCESS CHAMBER	850 (33-1/2")	730 (28-3/4)	1840 (72-1/2")			

DESIGN FEATURES

INTEGRATED EQUIPMENT



COMPANY PROFILE

Extract Technology has an engineering heritage of over 70 years. Providing clients with containment and aseptic solutions for pharmaceutical, biotechnology, research and development, nuclear, defense and radiopharmaceutical markets.

Walker Barrier Systems, now part of Extract Technology, was founded in 1943 serving the pharmaceutical industry since the 1960s and strongly established in nuclear and defense markets throughout it„s history.

As a leading manufacturer of isolators, downÌow booths and modular cleanrooms our driving motivation is **Delivering Innovation to Protect**.

Our manufacturing facilities are located in the UK and USA, ensuring the highest quality raw materials are used to produce robust and reliable Ïnished products for our clients.

At Extract Technology it is our responsibility to meet our clients„ changing demands with innovative, Ìexible solutions that enhance production in a safe, reliable and cost-effective way. Our ultimate goal is to contribute towards positively affecting patient lives.

> **We were hugely impressed by the response of Extract Technology's technical sales and support team in dealing with an extremely urgent request to provide specialist HEPA filters for our cleanrooms at Baxter Liverpool.**
>
> The Ïlters are business critical and downtime is measured in dollars per second. Extract Technology were able to provide ther correct Ïlters to site within 6 hours of the original request, a truly remarkable service.
>
> **Steve Dawson,** Process Specialist
> Baxter Healthcare Ltd

OUR MOBILE CLEANROOMS

Single, double-wide and modular unit connectors available. Increase height as required.

Flexible internal conÏguration

Extended mobile cleanroom personnel corridor

Internal Shots

Ceiling power
dropdowns as required

Maintenance walkways
available

LOCATIONS

SERVICES

- Mobile Cleanrooms (MCRs)
- Aseptic Isolators
- Cell Therapy Isolators
- Filling Line Isolators
- Sterility Test Isolators
- SteriPharm®
- C-RABS, O-RABS
- Containment Isolators
- Downflow Booths
- After Sales
- Service
- Spare Parts

CONTACT

UNITED KINGDOM

MATT PRIDDEN

Global Standard Products
Development Manager

E. matt.pridden@extract-technology.com
D. +44 (0) 1484 345 454
M. +44 (0) 7717 152 266

UNITED STATES

ANDREA BUNCE

United States Business
Development Manager

E. andrea.bunce@extract-technology.com
D. +1 (608) 350-8107

ACCREDITATIONS

CELL THERAPY SOLUTIONS

extract TECHNOLOGY

extract-technology.com

+44 (0) 1484 345 454

+1 (608) 562 7500

info@extract-technology.com

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