ISOLATORS

Solutions for pharmaceutical and biotech production

Why using an Isolator (closed system) rather than a Clean Room (open system)?

The evolution in the design of closed and automated systems for pharmaceutical and biotech production, be it classic (HPAPI) or Modern (ATMP), considerably reduces risks related to the safety of the product and the operator. **The use of isolators in the formulation, manipulation and production of biological drugs ensures the control of contamination with a high degree of confinement and represents an efficient solution to meet the demand for these precious medicines at relatively low costs.**

EUDRALEX Vol. 4, Manufacture of Sterile Medicinal Products, Annex 1 paragraph 4.3 states that:

> *"Restricted Access Barrier Systems (RABS) and isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS [Contamination Control Strategy]. Any alternative approaches to the use of RABS or isolators should be justified".*

So, according to this statement if, for a given system, the choice went to the use of a Clean Room instead of an Isolator, this alternative approach should be justified.

Another important statement in Eudralex Vol. 4, Guidelines on Good Manufacturing Practice, specific to Advanced Therapy Medicinal Products, paragraph 9.5.1, is the following:

> *"Production in a closed system, in an isolator, or positive pressure isolators: a background clean area of grade D is acceptable".*

10 good reasons to use an Isolator (closed system) rather than a Clean Room (open system) for the production of advanced therapy drugs (ATMPs)

1. Separation product/operator;
2. Installing a Grade A closed system in a class D;
3. Economic saving of the facility's operating costs of the order of 70%;
4. Easy control and monitoring;
5. Reduced space (- 47% used surface);
6. Quick and easy cleaning and decontamination;
7. Flexibility and process adaptability;
8. Traceability of the production process;
9. Bioconfined transfer systems;
10. More productivity, less stress for the operator.

Both these statements are important guidelines and **recommend the production of ATMPs in closed systems** (Isolators with work areas classified as Grade A) **installed in a Grade D Clean Room** ("AinD" closed system").

The possibility of installing Grade A Isolators in a Grade D environment **simplifies the operating procedures relating to personnel flow, gowning, validations**. Furthermore, **the infrastructure complexity and relevant costs are strongly reduced**, compared to the use of Grade A Biological Safety Cabinets (BSC, with inner classification ISO 4.8) inside Grade B Clean Rooms ("AinB" open system).

Another key point is that **the level of bio-confinement provided by an isolator** – *physical confinement* – **is much higher** compared to the use of BSCs, which just guarantees a *dynamic confinement*, provided by the inward front barrier through the front opening of the cabinet.

Last but not least, it has been proved that a closed system (AinD) allows, compared to an open system, **an economic saving of the operating costs of the facility in the order of 70% with same production output**.

Bioair solutions portfolio of systems and products in this sophisticated field of applications is very broad and specific. The most advanced product in the Bioair Isolators range is today the **ISOCellPRO® 4.0**, a specifically designed isolator for Advanced Cell and Gene Therapies, the company's flagship of the dedicated Bioair's Research & Development group for the pharmaceutical and biopharmaceutical production sector.

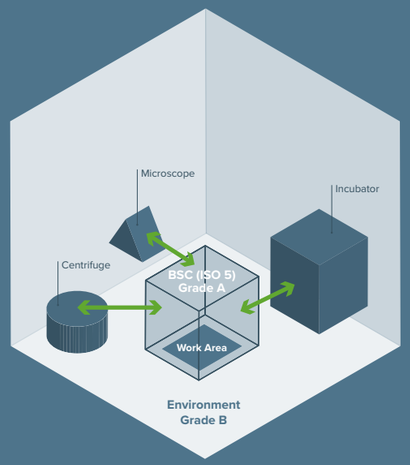
But, in the range of Bioair closed systems, other solutions are available that can satisfy various typical applications in sectors that require a strict bio-confinement.

This document illustrates their main features.

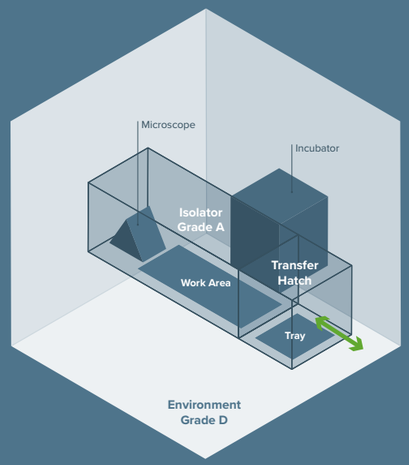
Open system (A in B) and closed system (A in D)

Isolators, closed systems, represent an advantageous alternative to use of Clean Rooms, open systems, for Advanced Therapies production.

Let's find out why.



Open system (A in B)



Closed system (A in D)

Most significant applications for the different series of Bioair Isolators

Applications	ISOMate®	ISOMateGMP®	ISOCellPRO®
Sterile Galenic Preparations	✓	✓	
Cytotoxic/CMR Substances Manipulation	✓		
Advanced Therapy products			✓
Gene/Cell Therapy			✓
Regenerative Medicine			✓
Sterility Testing	✓	✓	
GMP processes for pharma		✓	
GMP/pharmacological processes for hospital/lab	✓		
Oncology pharmacy unit	✓		

ISOMate® Series

Applications

- Sterile Galenic Preparations
- Cytotoxic/CMR substances manipulation
- Sterility testing
- GMP/pharmacological processes for hospital/lab
- Oncology pharmacy unit

Configuration/ more options

- 2 or 4 gloves
- 1 or 2 Pass-box
- Additional gloves for Pass-box
- Painted or full stainless steel versions

Control Systems/ optional

- VHP Sterilization system
- Particle and microbial counter
- Panel PC - SCADA module
- Glove leakage test system

Leak Rate Class/ 4

ISO 14644-7: 2004 e ISO 10648-2: 1994

The ISOMate® series includes various versions of entry level isolators, which meet the specific needs of applications such as sterility testing and handling of antiblastic products (oncology unit) in hospital pharmacies, etc.

These are “standard” isolators (the ISOMate series are therefore not generally foreseen for customization) however the range offers different variants, designed to adapt to various needs of use:

ISOMate® Cyto: Negative pressure isolator with bag-in/bag-out filter changing designed for handling of antiblastic, cytotoxic drugs, MAbs, R&D formulation of drugs and vaccines, manipulation of viral agents for diagnostic kits, etc.

ISOMate® Steri: Positive pressure isolator for sterility testing in a pharmaceutical environment, Grade A handling of products that require bio-confinement.

For both versions, It is possible to choose between options with 2 or 4 gloves, with an additional glove on the pass-through hatch for the transition between Grade D environment and the Grade A inner work area.
Pass-through hatches can be 1 or 2, connected to the Grade A work area. Another choice is between painted or full stainless steel versions.
ISOMate® can be equipped with **integrated VHP** with H_2O_2 concentration control.
The main functions of ISOMate®, including ventilation and door interlocking, **are managed by a PLC system**. As a further option, it is possible to integrate a **Panel PC that acts as a local SCADA module** that interfaces with the isolator control system, allowing control, monitoring and data recording in compliance with GAMP and FDA CFR21 part 11 requirements.
Leak rate of ISOMate® is class 4 (ISO 14644-7:2004 and ISO 10648-2:1994).

The ISOMate® series is not adaptable to URS specifications but is certainly configurable with some “on demand” changes if required.

ISOMate®: the right, competitive and fast choice for the pharmaceutical Quality Control laboratory, the research laboratory, the Hospital Pharmacy and many other applications.

ISOLATORS Solutions for pharmaceutical and biotech production

ISOMate GMP®

Applications

- Sterile Galenic Preparations
- Sterility testing
- GMP processes for pharma

Configuration/ custom

Control Systems/ integrated

Leak Rate Class/ 3

ISO 14644-7: 2004 e ISO 10648-2: 1994

The ideal solution for the use of closed systems in the pharmaceutical field, the “GMP” version of the ISOMate series, produced exclusively in full stainless steel, **provides a sophisticated tool for any GMP application, as a containment isolator** (negative or positive pressure) **for sterile biotechnological processes** (i.e. manipulation of viral vectors and cellular components such as DNA, research and preparation of vaccines, activities related to fill & finish operations on small volumes, etc, **in a GMP environment**.

ISOMateGMP® has a PLC monitoring and control system in compliance with **GAMP and FDA CFR21 part 11 requirements, based on a SCADA** - “Ignition” by Inductive Automation - consisting of a “WEB-based” supervision system well known for its scalability and wide spectrum of applications in various sectors and in particular in the Pharma industry, among other things, for the management of batch records and recipes development and editing
ISOMateGMP® is equipped with PLC controlled inflatable gaskets that guarantees Leak rate class 3 (ISO 14644-7:2004 and ISO 10648-2:1994).
An integrated VHP decontamination system is integrated in the unit and provides controls of minimum and maximum concentration of Hydrogen Peroxide.

ISOMateGMP® is a highly flexible designed isolator that allows the creation of entirely custom versions, based on URS issued by the customer (or developed together with the user) and with performances close to those of the superior series of Bioair isolators (ISOCellPRO).
A large choice of accessories is available, including RTP ports, sealed liquid transfer system (AT port) for connection to bioreactors, SIP/WIP, etc.
The ISOMateGMP is specifically designed for pharmaceutical and biopharmaceutical productions that require high safety standards in accordance with GMPs.
Its **flexible configuration** makes it suitable for different types of processes such as the manipulation of HPAPI, the formulation of vaccines, or the production of small-scale biological drugs (autologous samples), while maintaining high safety standards. The production processes that involve the ex-vivo genetic modification of cells (eg CAR-T), requiring that the processing part relating to the infection with the vector takes place in a confined environment, is another possible application for this flexible and highly customizable closed system.

ISOMateGMP: the GMP closed system solution designed according to your needs down to the smallest detail.

ISOCellPRO® 4.0

Applications

Advanced Therapy products

Gene/Cell therapy

Regenerative Medicine

Configuration/
custom, implementable with other systems and modular

Control Systems/
integrated

Leak Rate Class/ 3
ISO 14644-7: 2004 e ISO 10648-2: 1994

ISOCellPRO® 4.0 - **a clean room in 1m³** - is the ideal Bioair solution for the GMP production in closed systems (AinD), of ATMPs, Cell Therapy, Gene therapy, Tissue engineering and Regenerative Therapies, **designed to work within the typical restrictive boundaries of various regulatory bodies (FDA, EUP, USP) and related industry guidelines (GMP, PDA, Eudralex vol 4, Annex 1)**.

Now in its fourth generation, the ISOCellPRO® 4.0 has standard features that include an **"embedded" CO2 incubator,** the **integrated VHP system managed** by the SCADA, a **waste management** based on RTP, the **automated handling** of products and samples within the Grade A area, etc.

ISOCellPRO® 4.0 is therefore not a pure custom unit, but it **can be configured with various solutions and other specific add-on modules can be combined to the basic version** (second independent pass-box to avoid the "class jump", centrifuge module - refrigerated or not - refrigeration module, etc.) thus offering a properly modular system adaptable to the needs of the various application sectors.

ISOCellPRO® 4.0 has a **PLC monitoring and control system compliant with GAMP and FDA CFR21 part 11 requirements based on a SCADA** - "Ignition" by Inductive Automation - consisting of a "WEB-based" supervision system well known for its scalability and for its wide spectrum of applications in various sectors.

ISOCellPRO® 4.0 is equipped with **PLC controlled inflatable gaskets** that guarantees leak rate class 3 (ISO 14644-7:2004 and ISO 10648-2:1994).

Systems consisting of **multiple ISOCellPRO® 4.0** can be controlled by a SW architecture based on a server that operates as a **virtual machine**. Batch reports, audit paths and alarm logs are stored in a relational database on the same virtual machine in which Ignition operates or in a centralized storage. In this way, critical process points can be performed automatically using the typical IT methodology in total security: in this way in fact, a **hardware or software failure will not cause any data loss**.

ISOCellPRO® 4.0: a state of the art clean room in 1m3: all that is needed to develop advanced gene and cell therapies in a GMP environment in total safety, comfort and serenity.

Advanced therapies represent a continuous challenge not only for the improvement of the pathological conditions of millions of patients, but also for the development of innovative high-tech systems that allow the production of ATMPs in accordance with Good Manufacturing Practices (GMP).

The development of new generation technological solutions arises from the need to simplify the work flow of very complex processes in closed and automated systems.

The following table illustrates the classification of Advanced Therapy products.

ISOCellPRO®
Advanced Therapy Isolator

1. TRANSFER HATCH
from D (ISO 8) to A (ISO 4.8).
Sterilization with H_2O_2 vaporisation.

2. WORKING AREA
Grade A (ISO 4.8)
Airflow and Positive Pressure
Unidirectional airflow
Sterilization with H_2O_2 vaporisation.

A. Microscope
The working area with integrated microscope allow fast and easy observation without the need to leave the clean area.

B. CO_2/O_2 Incubator
The incubator is a custom device designed to fit into an isolator environment connected to the SCADA system.

C. Waste System
The bin is placed below the isolator and has an opening RTP port inside the working area.

D. Control System
Integrated SCADA managing system.

Classification of products of advanced medical therapy

Categories	Matrix	Products
Gene Therapy Medical Products (GTMPs)	Recombinant nucleic acids of biological origin	• Plasmids • Viral vectors • OGM • Gene-editing technology • Products of therapy derived from patients
Somatic Celi Therapy Medicinal Products (SCTMPs)	Manipulated cells and tissues to be used with a different function from the one of the donor	• Products containing human or animal cells and tissues • Tumoral immunotherapy • Autologue or allogenic cellular therapy • Living xenogenic cells • Stem cells and derived products
Tissue-engineered Products (TEP)	Manipulated cells and tissues (vital or not) to be used with a different function from the one of the donor	• Products containing human or animal cells and tissues • Products containing biomolecules, biomaterial and chemical substance • Stem cells and derived products
Combined ATMPs (cATMPs)	ATMP combination with therapeutic, prophylactic and diagnostic purpose	

Bio-confined Transfer Systems

IsoCellBIOBOX® Patented

IsoCellBIOBOX® is a unique, reliable, **GMP compliant**, low cost and easy to use **transfer system** that ensures the bio-confinement of cultured cells, under the same aseptic conditions as the Grade A working area of the isolator, to be placed in external standard incubators or other equipment.

IsoCellBIOBOX® is in fact a closed transfer system made in a special moulded plastic material resistant to thermal and/or chemicals sterilization cycles, equipped with an HEPA filter membrane that **allows gas exchange** (CO_2 and O_2) but **avoid the possibility of external particulate contamination** to enter the airtight container.

Inside IIsoCellBIOBOX® the cells contained in flasks, that have been prepared in the Grade A work area of the isolator, can be **safely transferred from the Isolator to standard external CO_2 incubators** in the Grade D area, keeping cells from different patients **safe from cross contamination and reducing drastically the equipment costs**, compared to other solutions that uses specially designed CO_2 Incubators (docking type or others).

Autoclavable and H_2O_2 Resistant

H_2O_2

Replaceable Hepa Filter

2 dimensions

L **391** x W **200** x H **161** mm

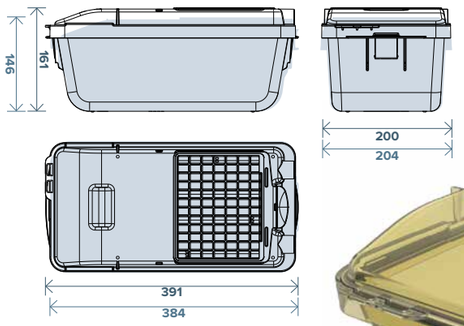
Flask
T25 n.**25**
T75 n.**9**

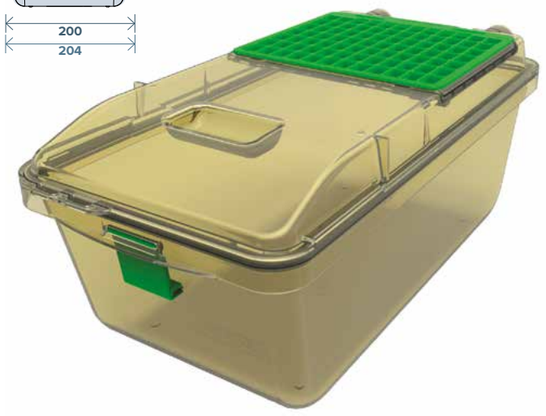
Tubes
15ml n.**22**
50ml n.**12**

L **384** x W **204** x H **146** mm

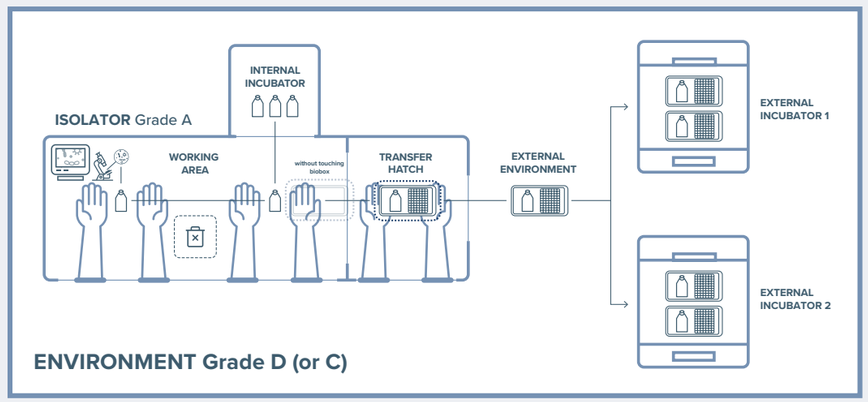
Flask
T25 n.**22**
T75 n.**7**

Tubes
15ml n.**18**
50ml n.**8**





The bioconfined systems used for the handling of the finished and semi-finished products in aseptic conditions, protects them from cross-contamination.



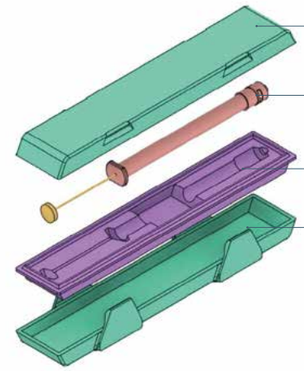
IsoSyrinGENE® Patented

Autoclavable and H_2O_2 Resistant

H_2O_2

Kit components of IsoSyrinGENE® and prototype section

IsoSyrinGENE® is a **sterile container for the bioconfined transfer of a microsyringe** containing the gene therapy drug from an aseptic environment (Grade A) to the operating room.
The syringe, which contains micro-volumes (50 µl) of gene therapy **must remain sterile** during the transport, and **must not be accidentally moved inside the box**, in order not to disperse its content.



1. Container lid (plastic transparent, autoclavable, high temperature resistant, reusable)

2. Micro-syringes (Hamilton type) contains 50 µl of therapy drug, preventing any movement and therefore any fluid dispersion

3. Syringe housing (plastic thermoformed, soft non-porous, sterilizable with Gamma rays, disposable)

4. Container base with airtightness clip (plastic opaque, autoclavable, high temperature resistant, reusable)

IsoCellBIOBOXβ® Patented

Sterilizable with H_2O_2 vaporisation

H_2O_2

Replaceable Hepa Filter

IsoCellBIOBOXβ® is a transfer system, based on the RTP concept, used for moving biological samples from Grade A area of the isolator to external standard CO_2 incubators, without interrupting the continuity of the bio-confinement of biological samples.

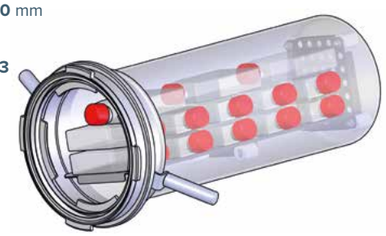
The main advantages of IsoCellBIOBOXβ® are:
1. Elimination of CO_2 incubators integrated in the isolator or external solutions, interchangeable and based on a docking system, very expensive and complex to manage;
2. Ability to work in a GMP environment with external standard CO_2 incubators located outside the isolator in the grade D clean room;
3. Optimal cell growth inside the IsoCellBIOBOXβ® when placed in a CO_2 incubator, thanks to the gas permeability (O_2 / CO_2) of the H14 filters placed at both ends of the container that facilitates the circulation of the gas inside the container itself.

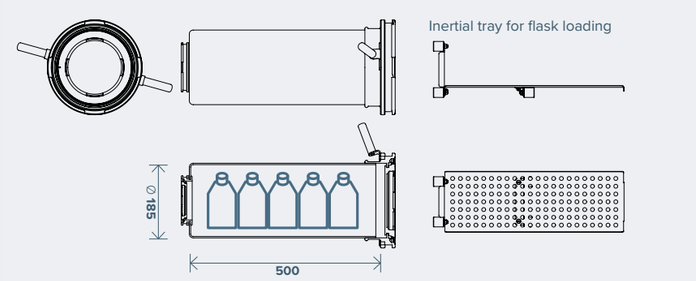
The **Self-propelled Robotized Trolley SRT** (Patent pending) for the automatic and robotic handling of IsoCellBIOBOXβ® is being studied. The trolley will allow transport from IsocellPRO to the CO_2 incubator of destination, and vice versa, using an integrated geolocation and wi-fi connection system, managed by the ISOCellPRO SCADA.

Dimensions

Ø **185** x L **500** mm

Flask
T75 n.**13**





Bibliography

Zanini C, Lando G, Severina F, Bonifacio M, *Indicazioni normative e guida pratica alla manipolazione delle terapie a base di anticorpi monoclonali*, ASCCA News – n. 1 January/March 2021

Zanini C, Severina F, Lando G, Fanizza C, Cesana E, Desidera D, Bonifacio M, *Good Design Practices for an integrated containment and production system for Advanced Therapies*, Biotechnol Bioeng. 2020 May 6. doi: 10.1002/bit.27376

Zanini C, Severina F, *White Paper "10 Good reason to use an isolator rather than a clean room for the production of Advance Therapy Drugs"* 2021, www.bioair.it

Cesana E, Bruschi E, Zanini C, Bonifacio M, *Manipolazione in sicurezza dei campioni di Sars-Cov-2: qual è la giusta cabina di sicurezza microbiologica da utilizzare?*, ASCCA News – Apri 2020

Zanini C, Rigamonti A, Severina F, Bonifacio M, *Confinamento biologico nella produzione di medicinali per terapie avanzate*, Notiziario Chimico Farmaceutico (NCF) – n. 4 May 2020

Zanini C, Severina F, Bastiani E, Bruschi E, Cesana E, Lando G, Camillo L, Desidera D, Bonifacio M, *Decontaminazione delle mascherine di tipo FFP2 ed FFP3*, ASCCA News – May 2020

Main references

Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta

Sistema Sanitario Regione Lombardia

CHUV Centre hospitalier universitaire vaudois

BMC Latvian Biomedical Research and Study Centre
research and education in biomedicine from genes to human

Incepta Incepta Pharmaceuticals Ltd

ACME For Health, Vigour and Happiness

ISOLATORS
Solutions for pharmaceutical and biotech production

We are

Bioair's history of research and development is characterized by more than 50 years of innovation. When, in 1972, the company, under the Gelaire brand, first launched in Europe what today is called a "Biological Safety Cabinet" or BSC, the very name of this equipment was not yet in common use. Then, in the 1980s, with the entry into force of the first International Standards for this type of product, our R&D department revolutionized the BSC control system of the time, designing the Compusafe, the first microprocessor developed specifically for Biological Safety Cabinets. Always one step ahead of the competition.
Over the years, always in line with the most significant developments in Environmental Contamination Control technology, always trying to "plan the future" and keeping faith with the company motto: your safety is our commitment, Bioair enters in increasingly sophisticated sectors and, in 2012, produces its first isolator for Advanced Cell Therapies.

Contact

Dr. Cristina **Zanini**
Scientific Manager
c.zanini@bioair.it

Ing. Franco **Severina**
Senior Technical sales engineer Isolators
f.severina@bioair.it

BIOAIR

Headquarter/
via Figino 20/22 - 20016 Pero (MI)
Manufacturing plant/
via Lombardia 12 - 27010 Siziano (PV)
ITALY
Phone: +39 0382 66721
www.bioair.it - e-mail: info@bioair.it

Bioair S.p.A.
via Figino 20/22
20016 Pero (MI) - ITALY
Phone: +39 0382 66721
www.bioair.it - e-mail: info@bioair.it