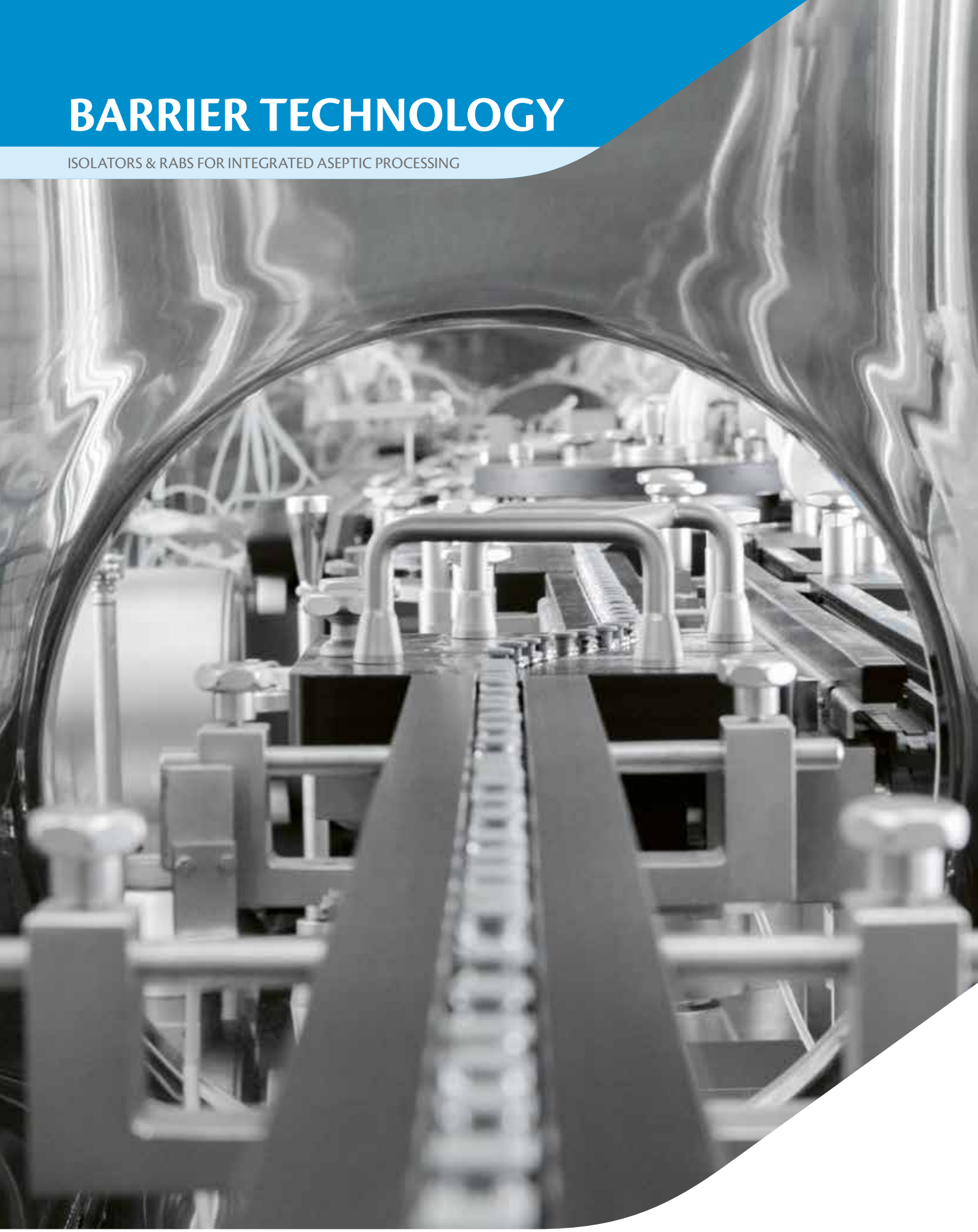
BARRIER TECHNOLOGY

ISOLATORS & RABS FOR INTEGRATED ASEPTIC PROCESSING



IMA LIFE

Aseptic Processing & Freeze Drying Solutions

ISOLATORS & RABS FOR INTEGRATED ASEPTIC PROCESSING

IN THE PHARMACEUTICAL SECTOR THE NEED TO PROTECT THE PRODUCT FROM CONTAMINATION DUE TO THE PRESENCE OF PERSONNEL OR THE ENVIRONMENT IS ONE OF THE MAJOR DRIVERS FOR CONTAINMENT.

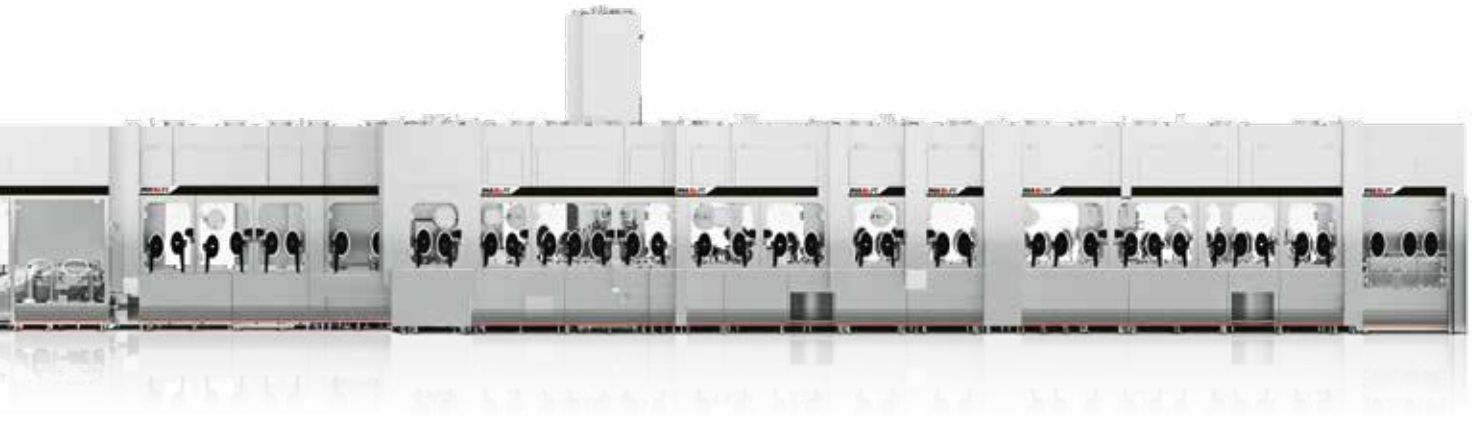
What matters most in pharmaceutical aseptic processes is the maximum reduction of the risk of product contamination which is basically due to particles and micro-organisms.
Combined with automated filling systems for liquid or powder products, isolation technology minimises direct human intervention in the processing area and is now a technology that is being rapidly adopted in the pharmaceutical industry. The use of this technology on filling machines offers obvious economic advantages as well as operating benefits while assuring greater product sterility. Fitting an unlimited number of modular layout configurations, IMA Life's isolated fill-finish solutions ensure the necessary versatility to adjust the production process according to customer needs and maximise line performance up to 600 units/min. with 100% In-Process Control. Incomparable flexibility and cutting-edge technologies featuring advanced robotics enable us to manage, via accurate no-touch transfer methods, a wide range of toxic and biological risk product types.

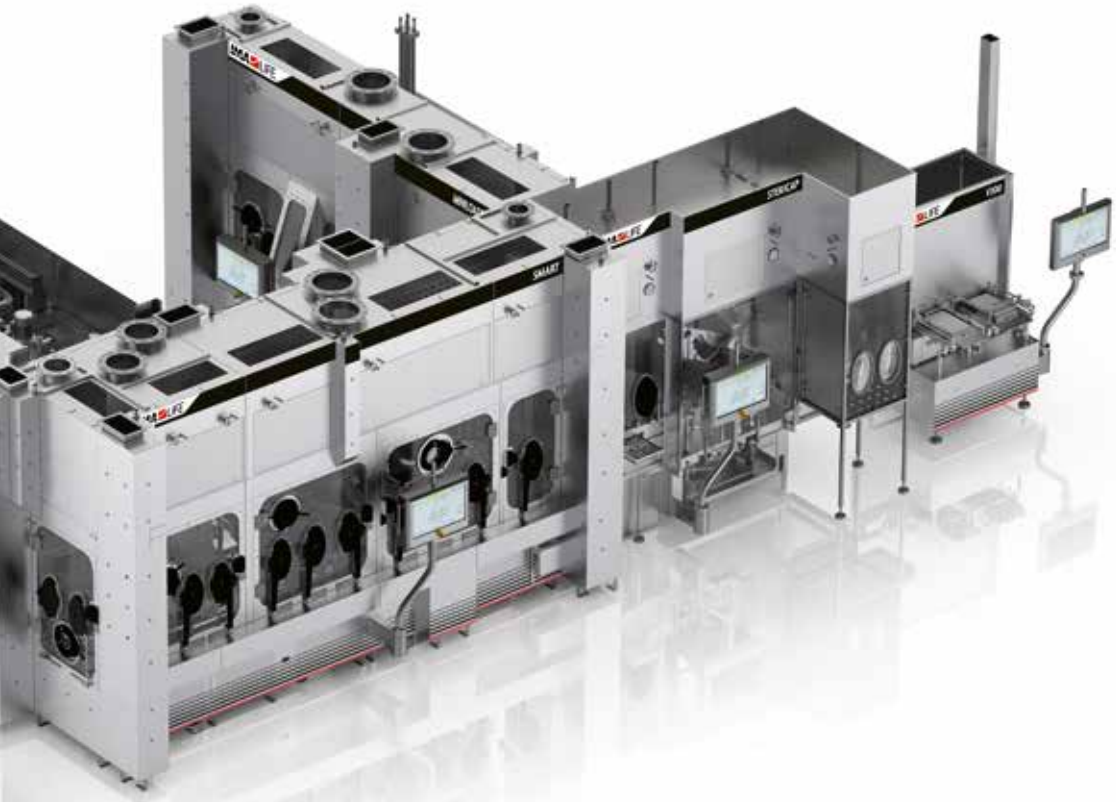
A variety of reliable containment solutions have been developed to meet customer's specific requirements. IMA LIFE can boast an in-house technology and wide range of applications, including:

- Isolators for aseptic and toxic filling lines for liquid and powder products
- Isolators for lyo loading/unloading systems for freeze dryers (aseptic and toxic)
- Sterility test and dispensing isolators
- Glove integrity testers
- Material Transfer Isolators
- Closed RABS
- Active/Passive Open RABS

A central matter driving IMA Life's research and development of highly specialised enclosed and aseptic processing systems focuses on preserving the integrity of pharmaceutical products, ensuring the maximum level of sterility and protection for both operator and environment.

IMA LIFE RANGE OF APPLICATIONS





UNIQUE POTENTIAL. INTEGRATED SOLUTIONS FOR PROCESSING EXCELLENCE

IMA Life designs tailored solutions to process liquid, powder and lyo products in an aseptic environment. The IMA Life range of isolators combines essential features and the simplicity of proven technology with widely appreciated high standards of quality and reliability.

ISOLATORS FOR ASEPTIC FILLING LINES

IMA LIFE ISOLATOR SYSTEMS ENSURE OPTIMUM OPERATOR AND PRODUCT PROTECTION AND FULL ISOLATOR-MACHINE INTEGRATION AS A COST-EFFECTIVE, EASY-TO-USE SOLUTION.

ANNEX 1 GUIDELINES

The isolator is now the preferred system for achieving maximum sterility assurance in fill-finish processes. The recent guidelines and the newly approved Annex 1 (EU GMP) strongly recommend the use of isolators as the best containment solution to reduce contamination risks in aseptic areas where critical steps of the fill-finish process take place and parts in direct or indirect contact with the sterile drug product are handled. The isolator reduces cleanroom classification requirements, avoids operator-related hazards and, when combined with the use of automated or robotic systems, simplifies operating procedures. Integrated with particulate and microbiological environmental monitoring systems, the isolator not only ensures the aseptic requirements in design and qualification phases, but also enables a comprehensive monitoring and implements the appropriate Contamination Control Strategy (CCS) required by regulators.
Furthermore, the increasing amount of toxic products treated by the pharmaceutical industry calls for more and more sophisticated containment technologies that can reduce the risks posed to operators and the environment and guarantee the basic requirement of patient safety.
Consequently, the use of cleanrooms for aseptic filling and processing is going to decrease, following an inversely proportional trend related to the isolator systems demand, which are best in handling specialty environments required by some of these products as low relative humidity or low oxygen levels.
Complete vial/syringe filling lines for aseptic and/or toxic products have been installed in several countries worldwide, in a fully sealed enclosure, equipped with a dedicated air circuit, where machines can be segregated. This system ensures the highest product protection and full operator protection. Production area can be downgraded to class C and is the ideal solution to handle highly toxic products.

OPERATION COST SAVINGS

- Less quantity of air required by the production room
- Less air sampling (particulate and microbiological)
- Less time spent by operators to enter/exit the classified room, and consequent increase of product protection
- Less expensive gowning

Internal view of an isolated aseptic filling line

IMA LIFE isolator systems provide the highest and most reliable machine configuration to grant:

- Highest SAL (sterility assurance level)
- Highest operator protection
- Highest automated operations

READY-TO-USE COMPONENTS AND ISOLATORS

The demand for greater flexibility has opened the way to the use of containers conveyed in Ready-To-Use tubs or trays, to be able to manage production in bottles, syringes or carpules on the same line and without labour-intensive format changing operations.
If RTU containers have to be placed inside the isolator, the No Touch Transfer system (NTT) provides a set of aerodynamic barriers and protective flows designed to protect the pre-sterilised primary container, and the area in which it is placed from particle, and microbiological risks. Isolator chamber design and pressure cascade configuration allow for the implementation of the No Touch Transfer (NTT) philosophy in the aim to improve product quality and eliminate human intervention.

Robotic arm handling
Ready-To-Use components

ISOLATORS FOR ASEPTIC FILLING LINES

TEAM FOR DECONTAMINATION CYCLE DEVELOPMENT, VALIDATION AND ENVIRONMENTAL CONTROLS

The IMA Life Microbiology & Process Sterility Assurance team is composed of process engineers and biological/pharmaceutical background members. The team is involved in each project from the very beginning for technical support and work alongside our customers whenever required.
Thanks to their 10 years' experience, the team has fulfilled many customer requests and carried out their activities directly on site with customers, conducting several VPHP validations. Based on their experience, the Sterility Assurance team can propose different VPHP validation approaches with cycle time optimisation, various studies for "worst case locations" and performance qualification. Moreover, the team can map the isolator's internal surface with VPHP low concentration analyser.

ISOLATION TECHNOLOGY KEY ELEMENTS

- Significant increase of SAL relative to conventional cleanrooms and open RABS
- Reduced risk of contamination during filling operation
- Humidity and temperature inside the isolator can be controlled adopting a dedicated HVAC
- The air used inside can be recycled, saving HVAC energy consumption
- Automatic, reproducible, well documented system for bio-decontamination for all critical machine parts in situ
- WIP (wash in place) cycles can be performed
- Automatic decontamination cycles (i.e. with VPHP) can be performed

THE SENTINEL PROJECT

IMA has always been committed to reducing the environmental impact of its equipment, addressing the issue of consumption through design choices, high-efficiency components and optimising the control dynamics on processing machines such as isolators. Several active projects are currently under development to exploit the advantages offered by advanced solutions for data collection and analysis in order to reduce consumption. These functions are part of the "Sentinel" project.

- Specific accelerometric sensors will be installed inside the isolators in order to monitor the ventilation motors and ensure they are functioning correctly.
- In the machines that are part of the fill-finish process (such as filling machines, vial washers, alu-capping machines), we will mount specific sensors to monitor electrical consumption.
- Additional sets of sensors will be provided for HVAC data collection.

The following table compares the amount of conditioned air required by the same filling line, installed in the same production room, but with different barrier technologies.

	Conventional CLEAN ROOM		OPEN or CLOSED RABS		ISOLATOR	
	Filling	Surrounding	Filling	Surrounding	Filling	Surrounding
Class	A	B	A	B	A	C
Clean room area m^2	68		41	27	20.6	47.4
Air changes per hour (considering the ceiling at 3 m)	-			60	-	40
Total air per hour	110,16	-	66,42	4,86	33,372	5,688
Total air per day (24 hours)	2,643,840	-	1,594,080	116,640	800,928	136,512
Total air per day (24 hours) in m^3	2,643,840		1,710,720		937,440	
Saving respect to an installation with conventional clean room	-		-35.29%		-64.54%	
Saving respect to an installation with OPEN or CLOSED RABS	-		-		-45.20%	

ISOLATORS FOR ASEPTIC FILLING LINES

IMA LIFE SOLUTIONS ARE FULLY COMPLIANT WITH INTERNATIONAL REGULATORY STANDARDS AND GUIDELINES (I.E. FDA, EMA).

MAIN CHARACTERISTICS OF IMA LIFE ISOLATORS

- Fully integrated isolator on machine base plate.
- Fully integrated design with equipment
- Easy access to the equipment's operating units
- Highly ergonomic
- Fast decontamination cycle: 2 hours with no load
- High-grade stainless steel construction
- GMP-compliant
- FDA-approved material
- Automatic leak test
- HEPA filters for air inlet and exhaust
- Air-handling system
- Pressure zone management
- Closed recirculation system
- Dedicated HVAC system (customised design, flexibility, modularity)
- Different VPHP validation packages: validation and cycle time optimisation
- One process philosophy and one design concept for both toxic and non-toxic products
- Configuration with air inlet from the clean room is possible
- Configuration with "one-pass" system (no air recirculation) is possible
- Configuration with fully nitrogen-based ventilation is possible

RAPID TRANSFER PORT (RTP)

Fixed to one wall of the isolator, the Rapid Transfer Port system (RTP) is a bi-directional contamination-free transfer system which allows for a wide range of sterile transfer applications into and out of an isolator.

The double-lid principle of the RTP technology is usually applied for the introduction in the Class A production area of:

- Pre-washed and pre-sterilized stoppers and alu-caps
- Petri plates
- Tools, change parts, etc.

Pre-stoppered vial collection for integrated lyo processing

HIGH TOXIC AND BIOLOGICAL RISK ASEPTIC PRODUCTION

- When reviewing the current offering of injectable products and related aseptic fill-finish lines, we increasingly come across configurations in which low-risk production for operators and the environment is mixed with high toxic or biological risk production processes.
- The focus on how to combine operational flexibility and high-risk products has grown in recent years due to the ever-increasing diffusion of personalised therapies, biological or biosimilar products and genome-specific treatments **(more generally referred to as ATMP)**.

HIGH POTENT AND BIOHAZARD PRODUCT HANDLING, SPECIFIC REQUIREMENTS:

- Design fit for containment requirements up to OEB 5, classified laboratories BSL-2 or BSL-3
- Option for automatic deactivation cycles with VPHP at production end
- Sloped equipment/isolator base plate to improve drainability
- Bag in - Bag out HEPA filters in return ducts in the case of toxic products
- WIP in air return ducts and in production section
- Spray nozzles & spray guns for isolator and equipment cleaning

Pre-stoppered vial loading into freeze dryer

ISOLATORS FOR ASEPTIC FILLING LINES

WALL DESIGN WITHOUT GASKETS BETWEEN ISOLATOR AND MACHINE BASEMENT ENSURING A PERFECT INTEGRATION AND LONG TERM HIGHER LEAK TIGHTNESS.

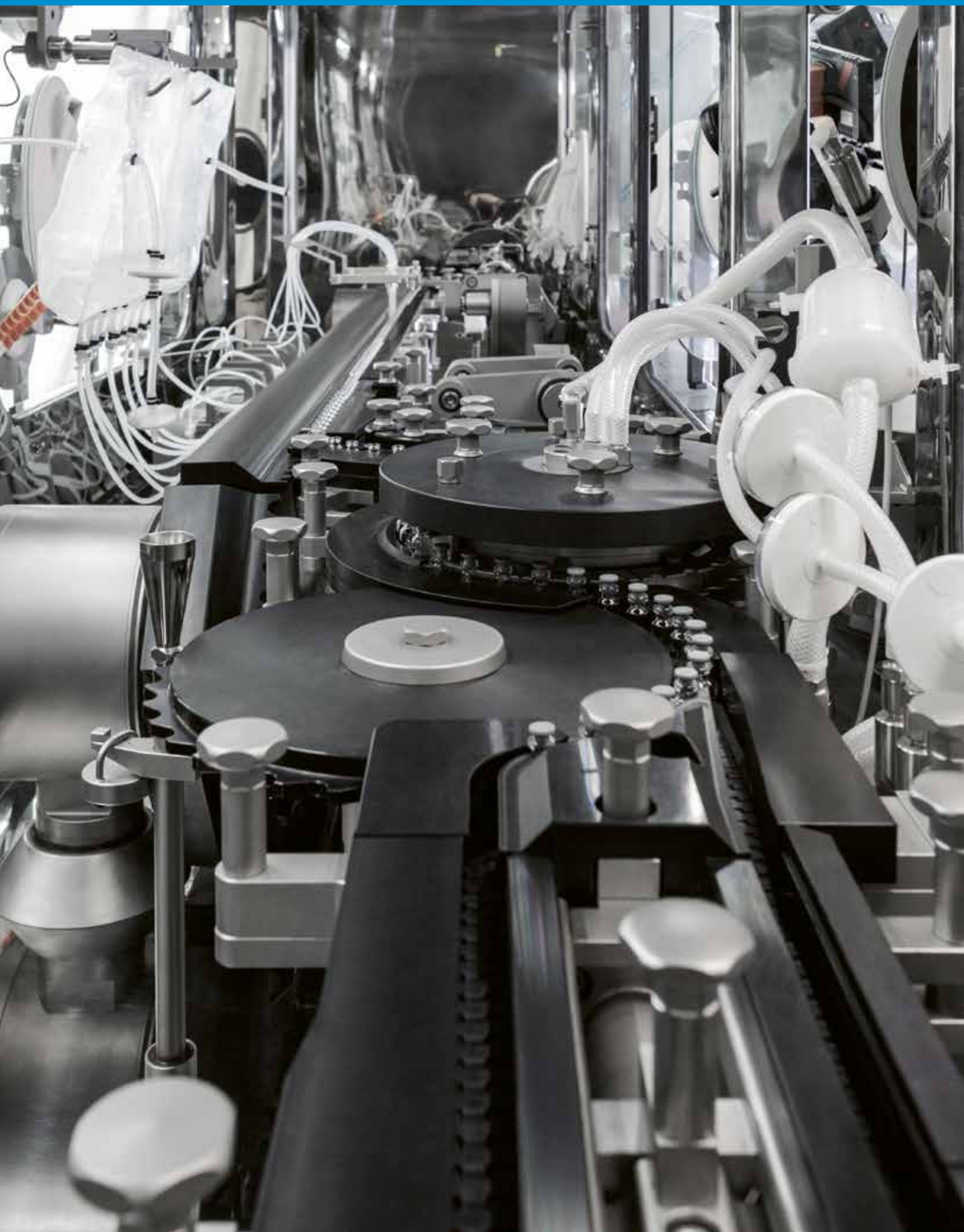
VPHP DECONTAMINATION CYCLES

Automatic decontamination cycles with VPHP systems are currently used as rapid, low-temperature techniques for decontamination of production filling lines, sterility testing isolators, sealable enclosures, and various types of pass-through systems within pharmaceutical production, research and bio-safety laboratory facilities.

VPHP DECONTAMINATION CYCLES CAN BE SUBDIVIDED INTO THE FOLLOWING STEPS:

- DEHUMIDIFICATION
- CONDITIONING
- DECONTAMINATION
- AERATION

IMA LIFE can supply a complete package that includes Cycle Development (CD) and Performance Qualification (PQ).



ISOTECH LAB: THE IMA LIFE IN-HOUSE ISOLATOR RESEARCH &

RESEARCHING THE FUTURE OF ASEPTIC PROCESSING AT THE IMA LIFE IN-HOUSE ISOLATOR RESEARCH & DEVELOPMENT LABORATORY

The new IMA Life IsoTech Lab is made up of the microbiological laboratory and isolator pilot room where we conduct R&D and customer-required tests. This enables us to increase decontamination process efficiency ensuring aseptic production quality in regulatory compliance.

Thanks to IsoTech Lab we are able to conduct several tests dedicated to new system technologies and VPHP cycle process optimisation. For example, engineering tests on atypical operating conditions (high temperatures or very low humidity) or load and machine component impact tests required by the customer, in terms of biological resistance and release of VPHP residues.

The isolator pilot room has three isolators complete with an internal filling line, a CLU machine for loading and unloading the freeze dryer and with a material transfer isolator (MTI), all in 1:1 scale.

The three isolators have dedicated equipment and utilities to simulate GMP environmental conditions inside them or to apply the specific decontamination process to create aseptic conditions.

All tests are performed using sophisticated and highly sensitive instruments (Picarro) also in collaboration with Italian universities and with the major industrial measurement companies.

DEVELOPMENT LABORATORY

THE IMA LIFE IN-HOUSE ISOLATOR RESEARCH & DEVELOPMENT LABORATORY HAS TWO MAIN OBJECTIVES

1. To perform internal research:
   - To optimise VPHP cycles;
   - To check the performance of electro-mechanical components of the HVAC circuits;
   - To make comparisons between VPHP generators and other sanitisation media;
   - To check material compatibility and resistance to decontamination agents.
2. To set up activities in conjunction with customers:
   - To check cycle times with agreed isolator loadings;
   - To perform preliminary training sessions for customer isolator management and VPHP development cycles.

STERILITY TEST AND DISPENSING ISOLATORS

STERILITY TEST ISOLATOR

IMA LIFE's production range also includes the ideal solution to perform Sterility Tests, drastically decreasing false positive results. Designed for QC Labs, pharmaceutical production and pharmacies, IMA LIFE's sterility test isolators are equipped with an unidirectional air flow system and guarantee a constant positive pressure gradient between the chambers and the external lab environment.

MAIN FEATURES

- GMP Class A ISO 5 isolator system
- Air quality assured by Ultra Low Penetration Air (ULPA U15), unidirectional down flow and return filters
- Isolator leak tightness test according to ISO 10648-2, CLASS 2
- Integrated sterility test pump
- Fully automated bio-decontamination procedure
- Fully integrated viable and non-viable monitoring systems
- Easy-to-use integrated glove leak testing system: requires no external piping, power or compressed air

DISPENSING ISOLATOR

Designed to meet the pharma industries requirements for highest containment levels during manipulation of potentially dangerous compounds for R&D, production and QC.

MAIN FEATURES

- GMP Class C ISO 7/8 isolator system
- Air quality assured by High Efficiency Particulate Air (HEPA H14) inlet and outlet filters
- Isolator leak tightness test according to ISO 10648-2, CLASS 2
- Fully automatic or manual WIP cycles available
- Rapid Transfer Ports or high containment Alpha/Beta valves to introduce and/or remove products from the isolator, without breaking the containment level.
- Easy-to-use integrated glove leak testing system: no external piping, power or compressed air required

Sterility test isolator

Dispensing isolator

GLOVE INTEGRITY TESTERS AND MATERIAL TRANSFER ISOLATORS

GLOVE INTEGRITY TESTERS

Nowadays, end users of aseptic filling lines are more conscious that glove leak testing is a fundamental procedure, in the direction of the Quality-by-Design approach. Our glove leak testing system is perfectly integrated into our aseptic filling line, providing a reliable and easy-to-use solution to glove integrity testing. The system is GMP-compliant and developed according to the international standard ISO 14644-7 Annex E5.

MAIN FEATURES

- GMP-compliant
- Completely wireless
- User-friendly and fully-automated system
- Reliable test results with relevant reports
- No need for external connections with compressed air or power cables
- Highly customised solution, suitable for any kind of port
- RFID technology for easy and safe management

Glove leak tester

MATERIAL TRANSFER ISOLATORS (MTI)

The MTI is recommended to decontaminate components, tools, or whatever unit is introduced into the isolated filling line, without breaking the aseptic environment. It is used to obtain a fast bio-decontamination transfer process. **It can be a section of the "main filling line isolator"or a stand-alone isolator.**
In both cases it can be decontaminated independently using VPHP ensuring a high level, aseptic environment.
The MTI ensures the highest air quality of the isolated environment thanks to:

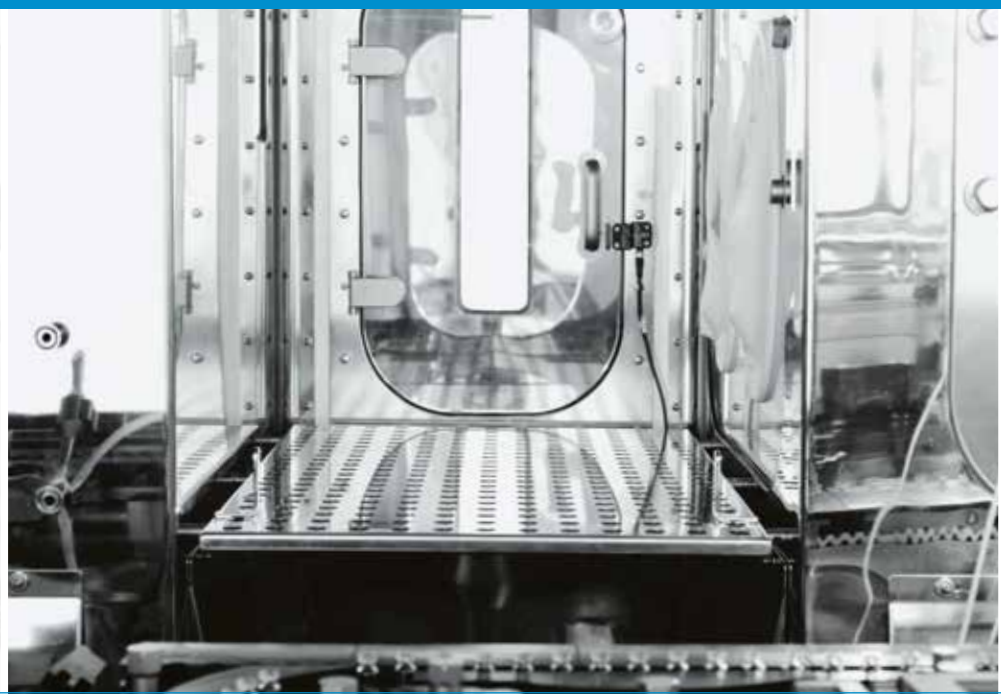
- an engineered filtration system composed of high-efficiency particulate air (H14) flow and exhaust filters;
- an integrated Vapour Phase Hydrogen Peroxide (VPHP) bio-decontamination system for very fast bio-decontamination cycles;
- inflatable seals made of FDA-approved white silicon.

MAIN FEATURES

- Ergonomic design to maximise operator's effectiveness and minimise accident risks
- Routine automatic leak testing system
- Low energy consumption throughout isolator Life thanks to the new sustainable low voltage ventilation fans
- Different standard dimensions
- The MTI can be upgraded with an Integrated Supervisory Control And Data Acquisition (SCADA) - iFIX with Historian Data Management Software

Material transfer isolator

CLOSED RABS



Material transfer Isolator - internal overview

RABS

The Restricted Access Barrier System (RABS), is a rigid protection made of transparent walls (polycarbonate or glass), equipped with an adequate number of glove flanges and gloves. It is installed on top of the filling and/or capping machines, separating them from the surrounding area.
Gloves must be positioned in order to allow the operator to perform all operations inside the machine, such as cleaning, caps/stoppers loading, vials removal, etc. so that these can be performed by operators without opening the protection walls.

CLOSED RABS

The closed RABS is an intermediate solution between isolators and open RABS. The unidirectional air flow (inlet and outlet) is fully controlled by the system, allowing a correct pressure control. The air is recycled and exhausted via a well defined channel, thus making this system suitable to be used with slightly toxic products.
Due to the lack of leak tight certification, these systems cannot be used for highly toxic products.
Class A environment must be assured whilst the surrounding must be classified as B.

MAIN CHARACTERISTICS

- Easy to validate (airflow, air classification, door interlocks)
- The production area can be downgraded to Class B
- Production area access control (doors can be interlocked)

Aseptic filling line under cRABS

Peristaltic pumps

- Automatic or semiautomatic WIP cycles
- Humidity and temperature inside the cRABS can be controlled adopting a dedicated HVAC
- The air used inside can be recycled, saving HVAC energy consumption
- Surrounding production area must be class B
- Limited operator protection: it is not fit for highly toxic products
- Performing automatic decontamination cycles (i.e. with VPHP) is not possible

OPEN RABS

OPEN RABS

A RABS is considered OPEN when the air used for the laminar flow is not recycled, but it is exhausted into the production room, without any control or filtration.

The open RABS can be either ACTIVE or PASSIVE:

- **ACTIVE**: it is equipped with an independent air ventilation system. In this case, the unidirectional airflow required is generated by fans and filters that are parts of the RABS itself. In both cases, the area inside the RABS must be "A" class, and the surrounding area must be classifies as "B".
- **PASSIVE:** it is not equipped with a dedicated air system. In that case, the unidirectional air flow inside the RABS should be generated externally by fans and filters embedded in the false ceiling of the production room.

In both cases, the area inside the RABS must be "A" class and the sorrounding area must be classified as "B".

MAIN CHARACTERISTICS

- Easy to install, also on existing machines
- Easy to validate (airflow, air classification, doors' interlocks)
- The production area can be downgraded to class B

Active RABS

- Surrounding production area must be class B (the isolator can be downgraded to the less expensive class C)
- No operator protection: it is not fit for toxic products
- Humidity and temperature inside the open RABS depend on the production room conditions
- Recycling the air used inside, saving HVAC energy consumption, is not possible
- Performing WIP cycles (wash in place) is not possible
- Performing automatic decontamination cycles (ie. with VPHP) is not possible

Passive RABS

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IMA S.p.A. reserves the right to make any changes to the described machine characteristics.

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