Isolation technology, securing contamination prevention...
A world of specialized resources

With installations in more than 100 countries, Getinge is a leading global provider of equipment and systems for contamination control in biomedical research and bio-pharmaceutical production environments. For our customers this means a number of obvious, basic benefits including expert resources, vast experience and local service support. We also have the capability to improve our clients’ productivity, quality and personnel safety, as well as comply with increasing regulatory demands.

When it comes to isolation technology, there are some specific benefits derived from our modular approach and the highly specialized knowledge from our subsidiary — Getinge La Calhène. These benefits are related directly to the quality of the customer’s process and the lifecycle economy of the equipment. The benefits are natural and logical, and they lead us to the definition of our basic mission: optimize our customer’s process without compromising quality or safety.

This brochure offers a brief description of the general principles of isolators use in research and production environments. It will also provide an idea of the challenges we have faced and addressed successfully over many years for our customers all over the world.
An instrumental force
During the late 1970’s La Calhène developed the first isolator systems based on years of experience in the nuclear industry. Since then, isolator technology from La Calhène has been used in many applications in biomedical research institutions and pharmaceutical factories all over the world. The company has introduced a number of innovations and has rightfully earned its worldwide reputation for being instrumental in the development of technology preventing cross-contamination between manufactured products and their environment.

An ingenious transfer system
The basic principle of isolation technology is simple: to separate a process from the environment. This may be done to protect the process from the environment (e.g. in the case of aseptic production) or the environment from the process (e.g. in the case of toxic material handling). Indeed in some cases it may be both – e.g. preparation of cytotoxic injectables (cancer treatment). The transfer of material into and out of isolators requires specific technologies. La Calhène is the originator and manufacturer of the DPTE® solution, also known as RTP or Alpha-Beta transfer ports. This ingenious device is now the gold standard for transfer of aseptic or toxic products in biomedical research institutions and pharmaceutical factories all over the world.

About La Calhène
- World leader in isolation technology with 3000 isolators delivered
- Market leader in transfer port solutions and accessories with 40000 units of DPTE® transfer ports in use worldwide
- A portfolio comprising more than 25 patents
- Worldwide customer references
- Manufacturing plant in Vendôme, France - implemented ISO standards

Getinge La Calhène: a complete portfolio

In 2005, Getinge Group acquired La Calhène. With this addition more than 30 years of global experience, a uniquely successful R&D and production culture was added to our global product portfolio.
Isolation technology

The basic principles

As a physical principle, isolation means the separation of a process – e.g. raw materials, a product or a laboratory experiment - from its environment. Reasons for this: to eliminate contamination from the environment to the isolated object, or vice-versa.

Two main alternatives

Today, there are two main methods of isolation. You can isolate an entire room – i.e. sealing it off from the environment outside. This is usually known as a “cleanroom” solution. As an alternative, a barrier can be placed just around the process. Two types of barriers are commonplace in the industry today: A Barrier Isolator or a Restricted Access Barrier System (or RABS). The essence of a Barrier Isolator is that it may be completely sealed, and may therefore be controlled and bio-decontaminated (usually using a chemical sterilant such as Hydrogen Peroxide Vapor). A complete production process may be contained within a series of isolators, thus separating the main contaminants (i.e. the surrounding facility and operators) from the process. The benefit of isolation technology is outlined on the following pages, but it is clear from the illustrations below.

The pressure factor

In production environments, the pressure inside the isolator is a key factor. Where the protection of the operator is a priority, a negative pressure will be maintained inside the isolator (any breach causing flow into the isolator, i.e. away from the surrounding process and operators). With conditions reversed, a positive pressure will be applied to protect the process.

Unidirectional and turbulent flow

Unidirectional (formerly known as “laminar”) flow occurs when a stream of airflows in parallel layers, with no disruption between the layers. Turbulent flow occurs when the flow layers are not parallel but take different, random directions: there is no specific flow pattern. An isolator is a sealed environment with control over potential sources of contamination entry (HEPA filters, transfer ports) and the absence of operators (the largest potential source of contamination). Under these circumstances, it is only necessary to maintain differential pressure (positive or negative according to application) using a forced ventilation system. i.e. turbulent airflow is sufficient and suitable to maintain a clean / aseptic condition and / or safe environment. Unidirectional airflow (which costs more to produce and maintain) is useful in specialised applications to ensure that particles are rapidly swept (in one direction) away from critical areas. i.e. it is appropriate to use unidirectional airflow in processes when mechanical equipment or material handling within the isolator produces particles which could contaminate the process.

Cleanroom

Green Zone = Grade B Area

Isolator

Blue Zone = Grade D Area
Rigid or soft wall

Isolators may be constructed in two styles. Rigid wall models have stainless steel or rigid plastic shells, while soft wall models use flexible PVC material. Both varieties have advantages and can be combined along the same production line. The final choice should be made after analysis of the specific operations in the application, which should include an assessment of failure risk and ergonomics.

Manual operations

Manual operations in an isolator are performed through glove-sleeves, half-suits or (less commonly) full-suits. These flexible extensions of an isolator allow for optimal ergonomics and freedom of movement while keeping the operator biologically outside the containment.

Isolator or cleanroom?

When using an isolator, only the environment inside the isolator needs to be controlled. In a cleanroom, the entire room must be controlled. Using an isolator has a number of advantages:

- With isolators, running costs are relatively low – sometimes as low as 20 percent of the costs of a cleanroom solution. Considerably less air has to be changed, which means reduced energy consumption and less environmental impact.
- In isolator systems, sources of contamination can be detected immediately. This traceability means minimized downtime and reduced false alerts. The process parameters are controllable.
- Isolators narrow the containment around the process by separating it from the outside source of contamination.
- The components in an isolator system are pre-tested resulting in reliability at a very high level and facilitated validation of equipment.
- In isolator systems, either unidirectional or turbulent airflow technique can be applied.
- In an isolator system, standardized, pre-tested components are combined into a customized overall solution.
- Relocation of isolators is easy.
DPTE® transfer solution
A crucial success factor

DPTE® transfer solutions provide the means to move material into and out of an isolator without breaking the containment. Within this field, La Calhène developed a solution that has become a gold standard worldwide. Originally built to transport radioactive material for the nuclear industry where Getinge La Calhène remains a key supplier, the DPTE® solution has been used for over 50 years for a wide variety of life science applications to transfer toxic or aseptic components without breaking containment. The DPTE® solution provides the highest bidirectional containment without intermediate bio-decontamination.
DPTE® - the functional principle

The system is based on the interaction of two separate units – Alpha and Beta – each fitted with a door, a lock and a sealing function. The Alpha unit is mounted on the wall of the isolator, while the Beta unit seals off the container or transfer isolator.

Picture 1 shows the container approach to the isolator and its Alpha unit.

Picture 2 shows the interlocking of the two units by a 60-degree rotation.

Picture 3 shows the interlocked doors being opened.
Safe transfer along the production chain

Optimal isolation safety requires scrupulous planning of the interaction between isolator technology, sterilization functions and transfer solutions – all of them fields of core competence within Getinge La Calhène. Below, you will find examples of equipment and systems developed to ensure safe transfer regardless of application.

DPTE® containers
Getinge offers a wide range of DPTE® Beta flange containers – autoclavable stainless steel containers, plastic containers (chemical sterilization) and flexible containers. Multiple designs and adaptability allows for an ideal solution in any field of contained production.

Liquid transfer
Transfer of sterile or toxic liquid products – is one of the most critical aspects of contained production. Getinge La Calhène can provide an unmatched experience within this field. Our concept is based on the DPTE® transfer system, now considered standard within the pharmaceutical industry.

DPTE-BetaBag® principle
The DPTE-BetaBag® is basically an integration of the DPTE® Beta flange and a bag for isolated transfer of sterile products or waste material. Size, shape and material vary according to component and production parameters. Filled with components, the bag can be sterilized (e.g. by Gamma irradiation) and made ready for connection to the filling line. The system offers safe, multi-use, bidirectional transfer (e.g. used bags can be used for waste removal). As an example, Getinge La Calhène can supply customers with a continuous supply of sterile components such as rubber stoppers and seals. This cycle can comprise all services from component packaging to feeding of the production line – including transport, sterilization, documentation, validation and recycling.

Closure Processing Systems (CPS)
As an alternative to the DPTE-BetaBag® sterile packaging solution for closures, Getinge can provide the CPS, a unique process for cleaning, sterilizing and siliconizing (optional) all types of pharmaceutical closures. The CPS offers an unbroken sterile chain from treatment to point of using DPTE® solution to transfer clean and sterile closures to the isolated filling line. Read more about CPS on page 13.

STERSTAR 2
Getinge provides STERSTAR 2 systems for continuous e-beam sterilization of tubs containing pre-sterilized syringes in the nest, at point of entry into a high speed filling line. The use of an e-beam allows rapid continuous sterilization without causing bottlenecks in the production flow (as is the case with batch sterilization) and guarantees a 6-log SAL reduction. Over 20 STERSTAR systems have been installed worldwide.
Isolators in the pharmaceutical industry

You will find below a comprehensive description of the production flow along the processing line in a pharmaceutical factory (using a production line for freeze dried cytotoxic products as an example). In order to illustrate the functional principles and the interaction between them, some simplifications have been necessary and a number of details have been omitted.

Stage 1 - Fine Chemical
The Active Pharmaceutical Ingredient (API) is typically produced as a powder and delivered to the fill-finish facility in a drum. The drum must then be sub-divided according to the required instructions. The API is typically highly potent/toxic and the operator must not be exposed to it during handling, a negative pressure isolator provides the necessary protection. Some API's are produced aseptically (e.g. suspension) and require bidirectional protection.

Stage 2 - Weighing-dispensing and Formulation
To obtain the required formulation, the product is typically dosed and diluted with a liquid carrier (WFI). The powdered ingredient is diluted to fill the required batch of vials. A negative isolator pressure must still protect the operator while the ingredients are dispensed to the formulation system.

Stage 3 - Filling and Packaging
The liquid solution is then ready to be sterile filtered and filled in vials (or syringes, cartridges etc.) in the filling machine. While still toxic, the focus is now on the protection of the product (maintaining sterility and contamination prevention). The filling line is placed within an isolator. Transfer from the filler to the freeze dryer is also under isolation, as is capping and inspection. All sterile closures, environmental monitoring devices, accessories and tooling are transferred using our DPTE® solution.

Stage 4 - Sterility Testing
After filling and capping, sterility testing is required to verify that the injectable product is indeed sterile. Samples are collected from each batch and are evaluated using a well-established procedure. There is a potential risk of contamination of the sample during the test itself, which would result in a “false positive” – indication of contamination when in fact there is none in the filled vial. False positive results are expensive, as investigation and reworking is required. Getinge ISOTEST has been developed specifically to minimize the risk of false results and make the procedure more productive/cost effective.
Efficient contamination control
in many applications

The benefits offered by isolation technology are to some extent identical regardless of application or operator/process protection – e.g. favorably low energy costs, traceability, minimized risk for false contamination alerts and the option of customized solutions by the use of pre-tested standard components. In many applications, however, a modular isolator system will offer specific benefits when it comes to equipment configuration, ergonomics, control functions and relocation flexibility.

**Biomedical Research & development units**
Within this sector Getinge offers the ISOLAB range of rigid isolators, developed specifically for small laboratory animals. Easy manipulation, absolute inlet and outlet filtration and optimal security are some major characteristics. Operation is possible under both positive and negative pressure, and the pressure will be maintained even when the containment is broken. Compatibility with the DPTE® system assures swift and reliable transfers. The fact that Getinge is able to provide surrounding contamination control equipment – e.g. autoclaves, cage washers, bottle washers, sterilizers, transfer elements and support tables – means efficient configuration and facilitated service & support.

**The biotech sector**
Many downstream processes in biotechnology require a combination of suitable working conditions and a validated barrier system eliminating cross-contamination between the product being processed and the surrounding environment. Getinge isolators are used for seeding, fermentation, centrifugation, filling and sterility testing in biotech plants all over the world. According to the process, they can work under positive or negative pressure. Integrated with DPTE® transfer systems they offer a bidirectional fully contained production line with optimal protection of both products and operators.

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*Biomedical Research and development*  
*ISOTEST in conjunction with an autoclave*
Closure processing system (CPS)
With a long-term involvement in sterilization and washing technology and a profound insight in pharmaceutical production methods, Getinge has developed a number of ingenious systems for specific needs. One example is the Closure Process System (CPS), comprising the entire aseptic production cycle for the closures (stoppers and crimp seals) used to seal vials of liquid or freeze dried products, or plungers (and needle shields) of prefilled syringes. This method ensures a low level of residual particles – due to efficient cleansing by sterile air and water and the elimination of friction by non-mechanical agitation. All types of closures can be treated.

Sterile packaging
Getinge’s range of sterile packaging products is assembled in our state-of-the-art cleanrooms. Ready-to-sterilize and pre-sterilized DPTE-BetaBag® and containers are available for a variety of applications including transfer of liquid and powder, caps, stoppers, vials, environmental monitoring kits, cleaning consumables etc. DPTE-BetaBag® are available in different diameters and volumes (from 10L to 150L) and materials (Tyvek™, EVOH/PE, PU).
The key factors:
Continuous control and routine monitoring

To ensure safety during the whole process, Getinge has developed a range of test equipment for routine monitoring of isolation components and transfer systems. If a failure should occur, the system makes it relatively easy to trace and detect. Traceability is one of the major benefits of using isolation technology. Getinge has also developed equipment for testing outside the isolators.

Transfer Leak Tester (TLT)
During contained transfer of materials into or out of isolators or aseptic container storage, leak-tightness must be at the same level as in the isolator. The TLT system is designed to check the integrity of the DPTE® transfer systems (both Alpha and Beta parts) prior to or after the production cycles. The control parameter is increased pressure. It is measured after connecting the DPTE® container to a vacuum chamber. The pressure is measured within 60 seconds after vacuum stabilization to eliminate the influence of shifts in temperature and atmospheric pressure. The total test is completed in 5 minutes.

Glove Leak Tester (GLT)
The isolator glove is the most vulnerable piece of the functions upholding the containment barrier. As such they need to be monitored for leaks and failure as part of the routine maintenance program.

The GLT and GLT2 systems have been developed for glove testing without breaking containment or otherwise interfering with the process flow. The tests are easy to operate and will detect perforations and faults in the gloves not visible to the human eye.

The GLT system works by exposing the glove to a reference negative pressure and then monitoring the presence of Oxygen. The test may be performed at any time, including during the operation of the isolated process. Multiple gloves and sleeves (up to 6) may be tested simultaneously using GLT2. Integrated Glove Leak Test systems are also available on Getinge’s isolators.
Bio-decontaminate the isolator: Various solutions are available

One benefit with isolators is the option to use bio-decontamination, thereby maintaining a germ-free environment regardless of operation. The process uses gas or vapor forms of chemical bio-decontamination agents. For years, Getinge has been a pioneer within this field of chemical bio-decontamination agents technology.

**STERITRACE 2** uses hydrogen peroxide \((H_2O_2)\) vapor (HPV) as sterilant. HPV is generated from liquid \(H_2O_2\) from a bottle that is placed in a receptacle on the isolator.

Developed by Getinge La Calhène, the integral generator is controlled by the same PLC as the isolator, minimizing components and requiring validation and maintenance of only one single piece of equipment. HPV is a proven sterilant, commonly used in pharmaceutical industry applications. It is compatible with most common materials, colorless, odorless and simple to monitor during equipment qualification. The container is fitted with an RFID device containing a batch number and expiration date of the liquid \((H_2O_2\) degrades over time). The generator checks if the date is valid and the batch number is recorded in the process report. Note: an external sensor is recommended for environmental/operator safety. Available from Getinge as an option.

**STERITRACE III - Noxilizer Inside** - uses Nitrogen Dioxide \((NO_2)\) gas as sterilant. Its on-demand technology generates Nitrogen Dioxide as needed, eliminating the need to deliver, store and manage sterilant on site. The gas allows rapid aeration to very low levels, which is needed when handling chemically sensitive materials. Gas concentration sensors are provided for real time process monitoring.
A complete range of innovative products

MODULINE™, a complete solution for filling line isolators
DARA, a company renowned for its flexible and reliable machinery, and Getinge La Calhène, the originator and driving force of the DPTE®, combined their expertise in filling lines, isotechnics and transfer systems to pave the way to one complete solution that is compact, modular and can be used for a wide range of applications.

ISOFLEX-R™ by La Calhène,
a state-of-the-art modular isolator
ISOflex-R™ is a completely modular isolator that is tailored to your specific needs and combines optimized ergonomics and efficiency. It is not only a one-size-fits-all isolator that can be very easily dismounted and pass through very narrow corridors. It can also equipped with the patented Isoturn bio-decontamination system that ensures H₂O₂ bio-decontamination in 10 minutes.

The revolutionary DPTE®-XO
After the Extra Secured DPTE®-XS, Getinge La Calhène, leader in DPTE® transfer system made a new step forward in leak-tight transfer, developing the externally opened DPTE®-XO, a new revolutionary DPTE® Alpha port that brings ergonomic benefits, eliminates particles and considerably speeds-up production with the absence of rotation of Alpha and Beta parts.

STERITRACE III - Noxilizer Inside
The STERITRACE III - Noxilizer Inside is a rapid bio-decontamination system that can be used for a wide range of our equipment. Developed with our partner, Noxilizer Inc, it is a flexible, modular system, allowing configuration to meet a wide range of bio-decontamination needs and can be integrated with our isolator systems to achieve a less than 12 minutes flash bio-decontamination time, using Noxilizer’s unique and innovative Nitrogen Dioxide (NO₂) process.


Testing

and documentation

From the design specification and through component selection, fabrication, assembly and Factory Acceptance Testing (FAT), all stages of the manufacturing process are examined and documented. Our documentation package ensures a strict quality control procedure in compliance with Good Engineering Practice. For our customers, it saves time and money along the validation chain.

In-process checking
In-process checks ensure that only the specified materials and components are being used. During assembly, a variety of inspections may be performed – e.g. leak and pressure testing, assembly operations and control of surface finish when applicable.

Documentation
The documentation package can be used as an integral part of the customer’s qualification material. It includes installation and user manuals, validation support documentation and technical manuals.

Factory Acceptance Testing (FAT)
Before installation, each product is tested according to a pre-agreed procedure. As an option, “prevalidation” of equipment can be performed at this stage. This means carrying out test procedures identical to the ones used for on-site validation. After installation, specialized technicians supervise the start-up and assist during the Site Acceptance Test (SAT).

Qualification
Our validation department will provide all-inclusive solutions for the qualification of equipment in accordance with all major international regulations. We also provide operator and technician training, tailored according to the application.
Instant, continuous support and service

Our core business idea could be summarized in one sentence: keep our clients safe and operationally effective. We spare no effort to obtain this. Everything we do must be related to this aspect of our customer relationship. Integrated solutions, continuous assessments and upgrades, well-defined quality systems and efficient service programs are some pillars of this philosophy. Rapid system integration, a high degree of technical compatibility and swift spare part delivery are others.

Installation, operation and performance
Long before the installation, experts from Getinge will develop detailed plans for the equipment configuration and the shipping logistics. In many cases, we will produce ergonomic models of the proposed solution and thus shorten the start-up time of new equipment considerably. In other cases, we will be able to “prevalidate” equipment before the actual validation, thus saving time and cost on site.

The Getinge Academy
The Getinge Academy offers a comprehensive range of training courses for professionals handling technical equipment in their daily work. Our catalog comprises the whole production chain within disinfection, sterilization and contained processing. Our focus is usually on operative and technical staff in the life science industries, but many of our courses will also provide engineering and marketing staff with useful information.
Innovative tools to help you make the right decisions

For many years, Getinge La Calhène has been investing a lot in R&D and also in innovative technologies to meet the needs of the market that are continuously growing and help you go far beyond your imagination to make the right decisions.

Thus, the company decided to develop the concept of the Virtual Isolator with the Virtual Reality team at CEA LIST.

The Virtual Isolator plunges the user – customer, designer, end-user or other participant – into a virtual world containing one or more isolators that he/she can interact with, in a highly realistic way.

Virtual Reality...

The dedicated Virtual Reality area in Getinge La Calhène’s Vendôme facility features an “immersive space” for Virtual Reality simulations on numerical models of isolators at Scale 1, which go well beyond simple visualization of geometrical data.

...close to the real world

zSpace® is an innovative display that allows users to complete complex tasks in a natural and intuitive manner and is ideal for training operators on our equipment.

Getinge La Calhène has developed innovative tools to help you go far beyond your imagination
Getinge Group is a leading global provider of products and systems that contribute to quality enhancement and cost efficiency within healthcare and life sciences. We operate under the three brands of ArjoHuntleigh, Getinge and Maquet. ArjoHuntleigh focuses on patient mobility and wound management solutions. Getinge provides solutions for infection control within healthcare and contamination prevention within life sciences. Maquet specializes in solutions, therapies and products for surgical interventions, interventional cardiology and intensive care.