GETINGE

GETINGE GROUP

GETINGE ISOLATION TECHNOLOGY
SECURING CONTAMINATION PREVENTION AND ENVIRONMENTAL SAFETY IN THE LIFE SCIENCES

Always with you

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: To 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.

GETINGE LA CALHÈNE!

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

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.

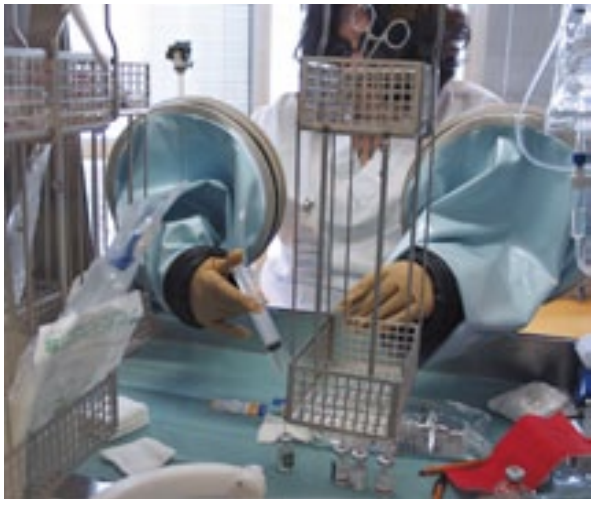
An ingenious transfer system

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® system, also known as RTP or Alpha-Beta transfer ports. This ingenious innovation is now the de-facto standard for transfer of aseptic or toxic products in isolators or RABS systems. Read more on this subject on pages 6 – 7.

About La Calhène

- World leader in isolation technology
- Market leader in transfer port solutions and accessories
- A portfolio comprising more than 25 patents
- Worldwide customer references
- Two manufacturing plants (Vendome, France & Rush City MN, USA) - implemented ISO standards



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.

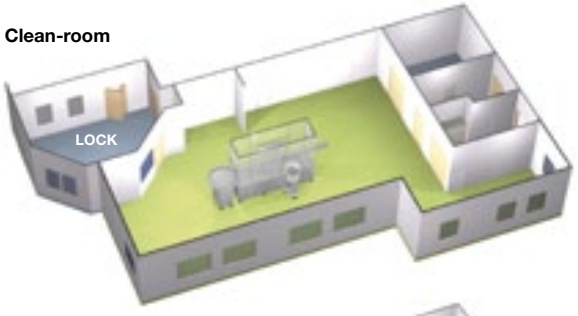
Two main alternatives

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 "clean-room" solution.

As an alternative, a barrier can be placed just around the process. Two types of barrier 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.

Clean-room



Isolator

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 air flows 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. ie. 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 flow in processes wheren mechanical equipment or material handling within the isolator produces particles which could contaminate the process.

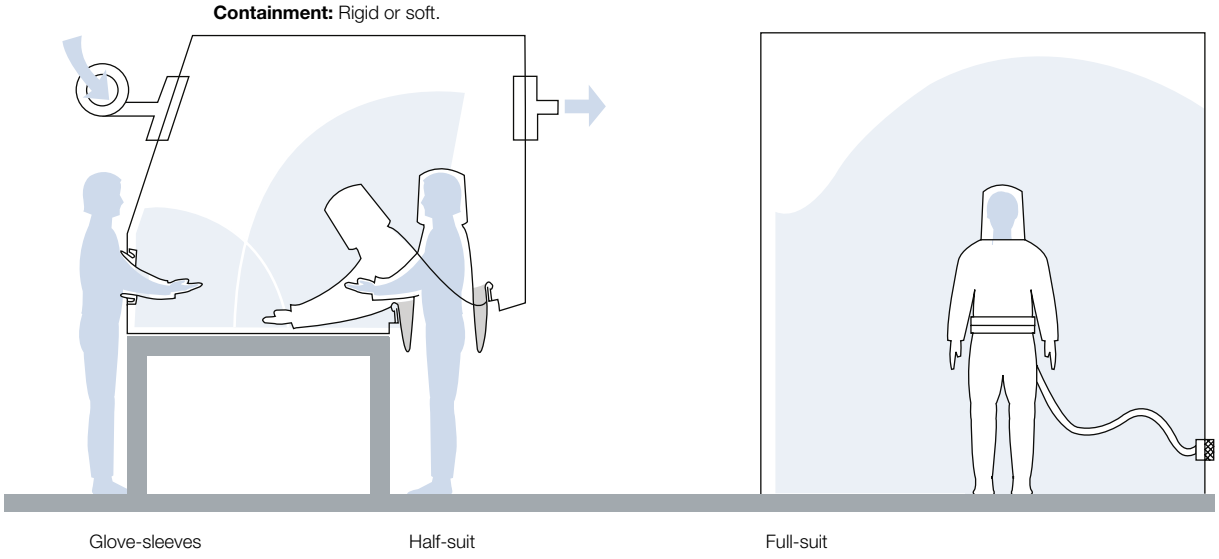
Rigid Soft

Rigid or soft wall

Isolators may be constructed in two styles. Rigid wall models have stainless steel or rigid plastic shell, 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-suit or (less commonly) a full-suit. These flexible extensions of an isolator allows for optimal ergonomics and freedom of movement while keeping the operator biologically outside the containment.



ISOLATOR OR CLEAN-ROOM?

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

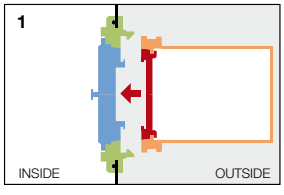
- With isolators, running costs will be relatively low – sometimes as low as 20 percent of the costs of a clean-room solution. Considerably less air has to be changed, which means reduced energy consumption and less environmental impact.
- In isolator systems, sources of contamination can be detected 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 flow technique can be applied.
- In an isolator system, standardized, pre-tested components are combined into a customized overall solution.
- Relocation of isolators is easy.

TRANSFER TECHNOLOGY – A CRUCIAL SUCCESS FACTOR

Transfer technology provides the means to move material into and out of an isolator without breaking the containment. Within this field, La Calhène developed a system that has become an industry standard worldwide. Originally built for transporting radioactive material for the nuclear industry (where Getinge La Calhène remains a key supplier), the DPTE® System is now also used for a wide variety of life science applications where toxic or aseptic material is being transferred. The DPTE® System provides the highest bi-directional containment without intermediate bio-decontamination.

DPTE® – the functional principle

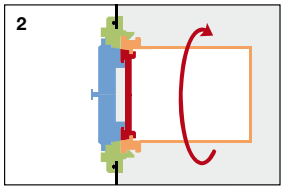
The system is based on the interaction of two separate units – Alpha and Beta – each fitted with a door, a lock and a sealing function. The Alpha unit is mounted on the wall of the isolator, while the Beta unit seals off the container or transfer isolator.



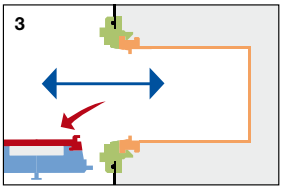
ALPHA

BETA

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. 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.

Bagging systems

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, bi-directional transfer (e.g. used bags can be used for waste removal).

As an example, Getinge 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.

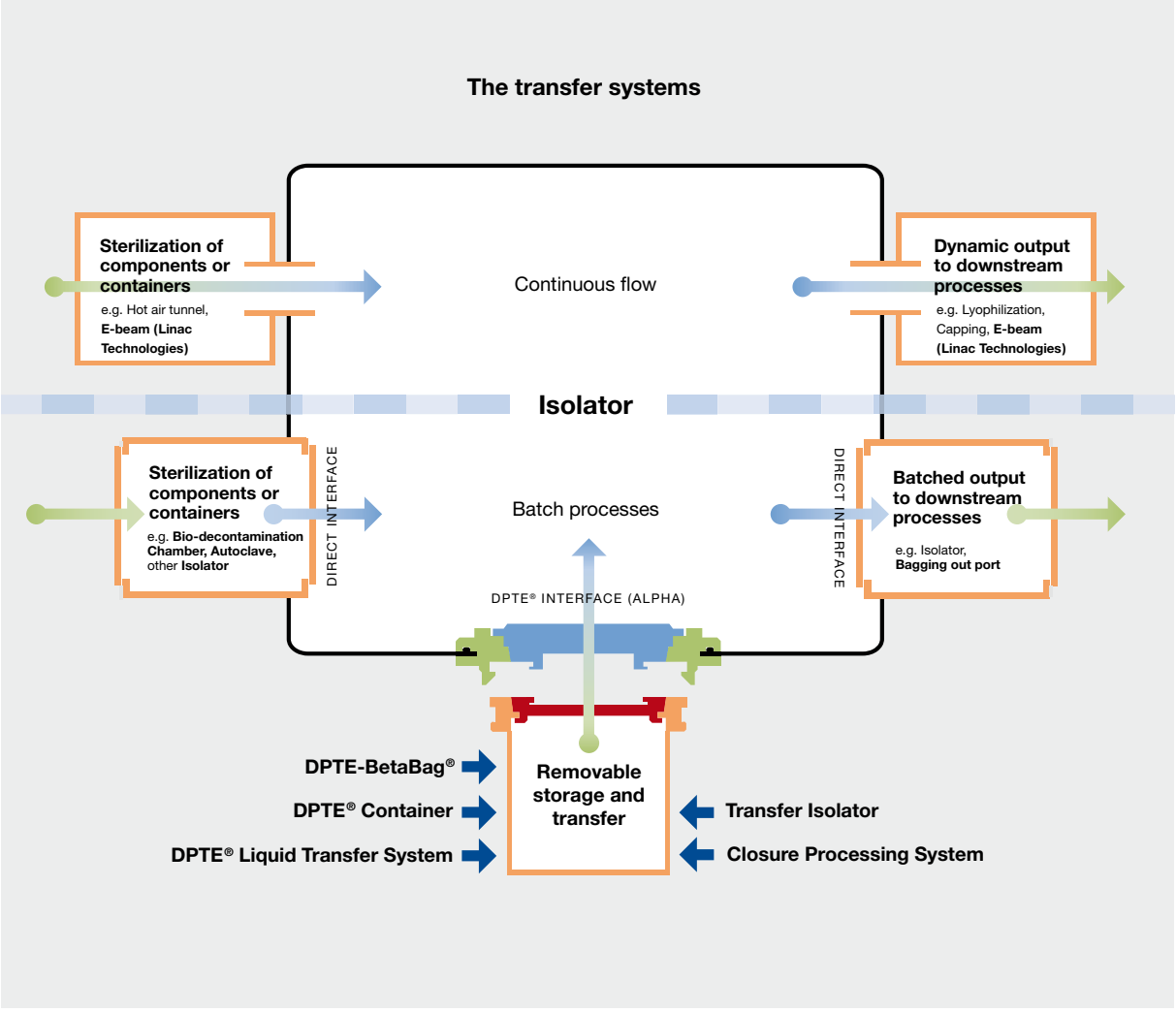
E-beam systems

Through our specialist subsidiary – Linac Technologies – Getinge provides systems for continuous E-beam sterilization of components, medical devices and pharmaceuticals. The use of an e-beam allows rapid continuous sterilization without causing bottlenecks in the production flow (as is the case with batch sterilization).

Different E-beam energies are used in different applications, for example, low energy (KeV) E-beam is used for surface bio-decontamination of components entering an isolator (e.g. pre-packaged sterile syringes). Higher energies (MeV) are used for terminal sterilization of pharmaceuticals and medical devices.

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® technology to transfer clean and sterile closures to the isolated filling line. Read more about CPS on page 11.



ISOLATORS IN THE PHARMACEUTICAL INDUSTRY

On the following pages, you will find a comprehensive description of the production flow along the processing line in a pharmaceutical factory (using a production line for lyophilized cytotoxic product 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 bi-directional protection.

Stage 2 – Weigh-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 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 lyophilizer is also under isolation, as is capping and inspection.

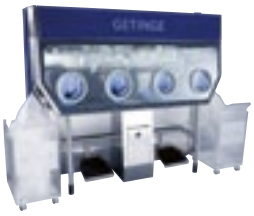
Stage 4 – Sterility Testing

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.

Hospital Pharmacy

Lyophilized drugs must be reconstituted locally (i.e. at point of use) before injection. For cytotoxic drugs, this procedure is hazardous for the doctors / pharmacists, as the drug product remains toxic to healthy humans. (Studies have shown that even when using protective clothing and safety cabinets, there is a risk for the personnel to be contaminated with the drugs).



Today, our ISOCYT systems for drug compounding and reconstitution in hospital pharmacies are widely used all over the world. Now, we present the latest addition to the ISOCYT series – the Getinge ISOCYT FREJA. A compact and productive system that provides the same sterility assurance level as in pharmaceutical manufacturing. A really safe and cost-efficient solution, that also offers better ergonomics, easier installation and lower operating costs.


GETINGE

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 bi-directional fully contained production line with optimal protection of both products and operators.

Biomedical Research and development

Biotech

Hospital pharmacies
Reconstitution of cytotoxic drugs is increasingly being performed in highly specialized central hospital units. In order to protect both the drug and the operator, a combination of positive and negative pressure is required. Getinge ISOCYT-series is a freestanding rigid wall compounding isolator for safe reconstitution of cytotoxic drugs. It has a leak-tight barrier and an efficient bio-decontamination system.

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 lyophilized 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
As an alternative to a rigid container, bags may also be fitted with a DPTE® Beta port. This ingenious container – or DPTE-BetaBag® – may be used for the sterile transfer of all kinds of components. Getinge La Calhène maintains clean room facilities for the aseptic filling of bags with components, which may then be sterilized using gamma irradiation. Components may then be delivered and aseptically transferred directly to point of use. Unlike competitive alternatives, multiple transfers may be made and when empty, the bag may be used for waste disposal.

Hospital pharmacies


Closure processing system (CPS)


Sterile packaging – DTPE-BetaBag®

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.

TLT – Transfer Leak Tester

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 prior to or after the production cycles.

The control parameter is increased pressure, measured after connecting the DPTE® container to a vacuum chamber. After the vacuum is stabilized, the pressure
is measured within 60 seconds to eliminate the influence of shifts in temperature and atmospheric pressure. The total test is completed in 5 minutes.

GLT – Glove Leak Tester

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 maintainance 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.

The GLT2 system works by monitoring pressure changes (pressure decay) and is performed before and after operation of the isolated process. Multiple gloves and sleeves (up to 6) may be tested simultaneously using GLT2.

Efficient isolator bio-decontamination

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.

ISOVAP is a semi-automatic sterilizer using the principle of in-line evaporation of a liquid bio-decontamination agent. The vapors of the agent are carried into the isolator by compressed air and evacuated via the exhaust duct. Isolator pressure and the temperature of the evaporation stream are controlled continuousl offering efficient monitoring of the bio-decontamination process.

STERITRACE II uses hydrogen peroxide (H2O2) vapor (HPV) as sterilant. HPV is generated from liquid H2O2 from a bottle which 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 a single piece of equipment.

HPV is a proven sterilant, commonly used in pharma-ceutical 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 (H2O2 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 required for environmental/ operator safety. Available from Getinge as an option.

Inoculated germ carriers
Germ carriers inoculated with bacterial spores are used to validate the sterilization cycles or the decontamination of isolators used in aseptic production processes.
The design and fabrication of the spore carrier, and the preparation of the spores, is critical to the efficient and proper process validation.

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, every 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

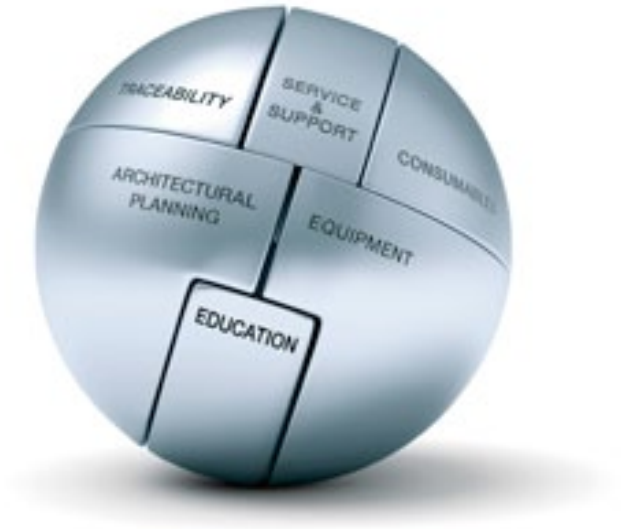
Our core business idea could be summarized in one sentence: To keep our clients safe and operationally effective. We spare no effort to obtain this. Everything we do must be related to this aspect of our customer relationship. Integrated solutions, continuous assessments and upgrades, well-defined quality 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.



COMPLETE SOLUTIONS FOR CONTAMINATION PREVENTION

Getinge is the world's leading provider of solutions for effective cleaning, disinfection and sterilization in the healthcare and life science sectors. We are dedicated to helping our customers provide maximum productivity in the most cost-efficient way. We do this by offering well thought through and customized solutions. This means that we are with our customers all the way from architectural planning and education to traceability and support – with complete solutions, long-term commitment and global presence. Getinge – Always with you.

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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.