

Chapter 2

Isolators for Personnel- and Environmental Protection

Personnel protection isolators are increasingly replacing the personnel protection clothing, which is needed to enter process plants that are classified hazardous for operators. Full protective suits have the disadvantage that they are expensive in purchase and reconditioning and time-consuming changes for the operator are necessary. Furthermore, the environment cannot be effectively protected from the release of problematic chemicals. The protection of the environment, the employees, and the products can be done much easier with the use of tight isolators in which the process takes place. The active ingredients in the form of dust particles of different sizes can't escape and do not reach the skin and respiratory tract of the operators and the surrounding room. If there are minor leaks, the concentration of the hazardous substances is markedly reduced.

The required performance of the containment depends on the substances to be processed. The materials must be individually defined by the manufacturer and classified according to local standards. In Germany, for example, there is the Hazardous Substances Act (Gefahrstoffverordnung, GefStoffV) and the Chemicals Act (Chemikaliengesetz), as well as operator exposure limits (OEL) and recommendations of the professional association for the handling of hazardous substances [1]. Internationally is often the definition Occupational Exposure Limit (OEL) used. In the pharmaceutical industry products and processes are classified according to so-called Occupational Exposure Bands (OEBs). The handling of hazardous substances from the perspective of a pharmaceutical contract manufacturer with a decision finding tree can be read in [2].

In the future, it is the Globally Harmonized System of Classification and Labeling (GHS). Based on an initiative of the United Nations (UN), the European Union (EU) plans a uniform labeling of chemicals (EU Directive 67/548, EU Regulation 1907/2006 "REACH Regulation"). The goal is a globally harmonized system for classification of chemicals including labels and safety data sheets. With a globally applicable classification method with uniform pictograms and text for dangers, the risks to human health and the environment during production, transport, and use of chemicals or hazardous substances are minimized worldwide. From

the end of 2010, the GHS labeling requirements for substances is binding, from 2015 on for preparations too. In the transition period, the old safety identification must be also specified in the material safety data sheet.

2.1 Personal Protection Isolators in the Pharmaceutical Industry

The production of tablets and capsules of cytotoxic drugs and hormones is a major application for containment systems (Fig. 2.1).

In this process, several steps can be contained by a glove box or an isolator. Starting from the wet cake a centrifuge discharge can be done via a glove box. The vacuum dryer can be contained by a loading and unloading isolator in front of the dryer. The mill and the sifter can be completely encased in an isolator. After

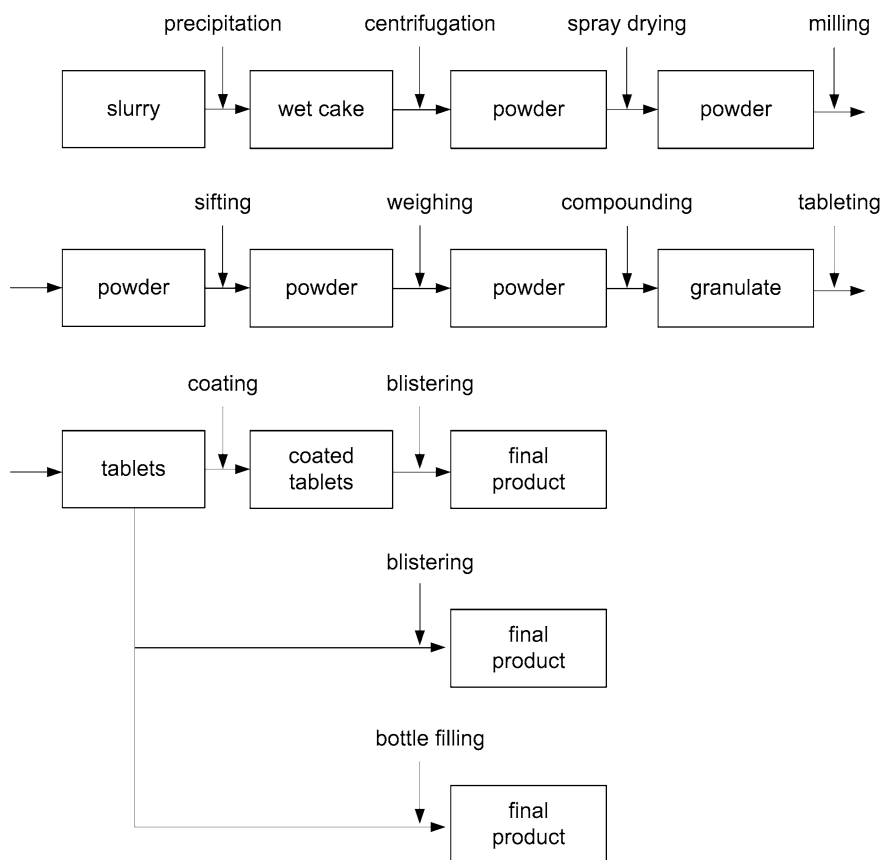


Fig. 2.1 Possible process for a tablet production with highly active substances

sifting, the powder can be packed in a packing isolator into an endless liner (see [Sect. 6.1.8](#)). From there it goes to the weighing and compounding isolator. Additives and excipients are added in the compounding isolator, and the whole preparation is transferred to a mixing device. From mixing to granulation, mostly vacuum transport is used. From the granulator, the granulated product is transferred to the tablet press. The tablets are collected in an intermediate bin after passing the deduster and the check for metallic impurities. For this step, a discharge isolator with the possibility to take samples can be used.

If the tablets are coated, the risk for the operator and the environment to be contaminated is low, so lower protective measures can be taken. If the tablets are uncoated, the blister machine or the bottle filler should also be considered being in isolation. To fulfill the different tasks, several different types of isolators have been constructed and are consecutively described.

2.1.1 Single Use Isolator (Soft Wall)

An alternative to the traditional stainless steel isolators provide flexible single use isolators. Single use isolators are used for transferring and weighing of hazardous powders and granules from containers with liner, for example, from drums into smaller sizes or better manageable container. Also probes can be sampled in this manner. When the application is frequent product change, as for example in multi-process-systems, these types of primary containment systems are particularly suitable.

Disposable isolators consist of a foil isolator and a basic stand on casters. The base frame with a height adjustable support surface is equipped with ports, counter rings, and inflatable seals for the connection of a transfer container. The foil isolator is fixed with an expander in the frame. The entire system is closed and constructed in accordance with GMP requirements and therefore suitable for use in clean rooms. The control panel with scale terminal and pressure monitoring is fitted directly on top of the isolator. The isolator is made of FDA-compliant LDPE film and has, like the base frame, two ports: larger one for drums, and a smaller one for connecting plastic bags. On the front of the isolator are glove ports to ensure that all operations in the isolator can be performed easily. In addition, the flexible film isolator has two filter cartridges for the supply of nitrogen or clean air, an exhaust filter (filter class H13) and a scale decoupling with a support stand (passive weighing unit) for the weighing bowl and two inside pockets integrated for housing the equipment (rounded scissors for foil cutting, shovel). Disposable technologies are still a relatively new technology for containments. But they offer some advantages over established systems that come in use for many applications. In addition to the relatively low investment cost, recurrent costs for the replacement of the disposable tents and special waste disposal of the used foil have to be calculated. On the other side, there is no need for complicate and time-consuming cleaning validation of the system after use, because the used film isolator is

disposed as hazardous waste. The risk of a nonappropriate cleaning is not given. Adhering to the principle of isolators, the system is at any time closed and provides an effective personnel protection. Foil changes with each product change avoid the risk of cross contamination.

A foil isolator can be repeatedly used for products of the same production batch. After the first use of the system, it is closed at any time due to the residual foil on the ports (foil protective hoods). No product can leak out. In the operating state of the isolator, it is uniformly flushed with nitrogen or ultrapure air. After inflation, it is operated at a constantly negative pressure from -30 to -20 Pa, to prevent particles from getting to the outside. With a sufficient HEPA filtered flushing medium, the clean room class D can be achieved. It is pressure controlled by the exhaust fan and an adjustable secondary intake air connection.

For metering and weighing the product level for refilling in an active and a passive unit, the integrated scale is divided by the flexible film isolator. The evaluation processor unit is outside the foil isolator, the passive weighing bridge is inside. Weighing with an accuracy of ± 2 g is possible. Different pressures can be set in the isolator and do not affect the weighing accuracy. Due to the lack of an own potential ignition source, the use in hazardous areas is possible.

The isolator can be operated with an electro-pneumatic control for inflation of the gasket, inflate the foil tent, evacuation of the tent after use or optional nitrogen flushing. The electrical cabinet mounted on the side of the base frame is easily accessible to the operator. The balance, the exhaust air, or intake air are positioned in a way that the user is not disturbed during transferring and weighing of bulk materials (Fig. 2.2).

2.1.2 Isolators for the Production of Highly Active Ingredients

Isolators to ensure the operator health and safety (Fig. 2.3) are used for discharging or filling of bags and containers, for the sampling within process systems or for the preparation and filling of tanks. Other applications include reactor discharge, vacuum drying with a flanged oven, milling, sieving, and packaging. Due to the strict separation of personnel and product, there is secondly also the product protection given. Special processes may also require explosion-proof designs. Further application is the handling of allergenic, teratogen, or carcinogenic material.

The functional working chambers made of stainless steel with rounded corners are usually mounted on a stable support structure with height leveling legs or hanging from the ceiling in the process plant. A media panel, mostly integrated in a side wall of the containment made of sheet steel, can be retrofitted with media pipes or electrical penetrations into the isolator chamber. To illuminate the working chamber without blinding, a light source is installed on the ceiling of the

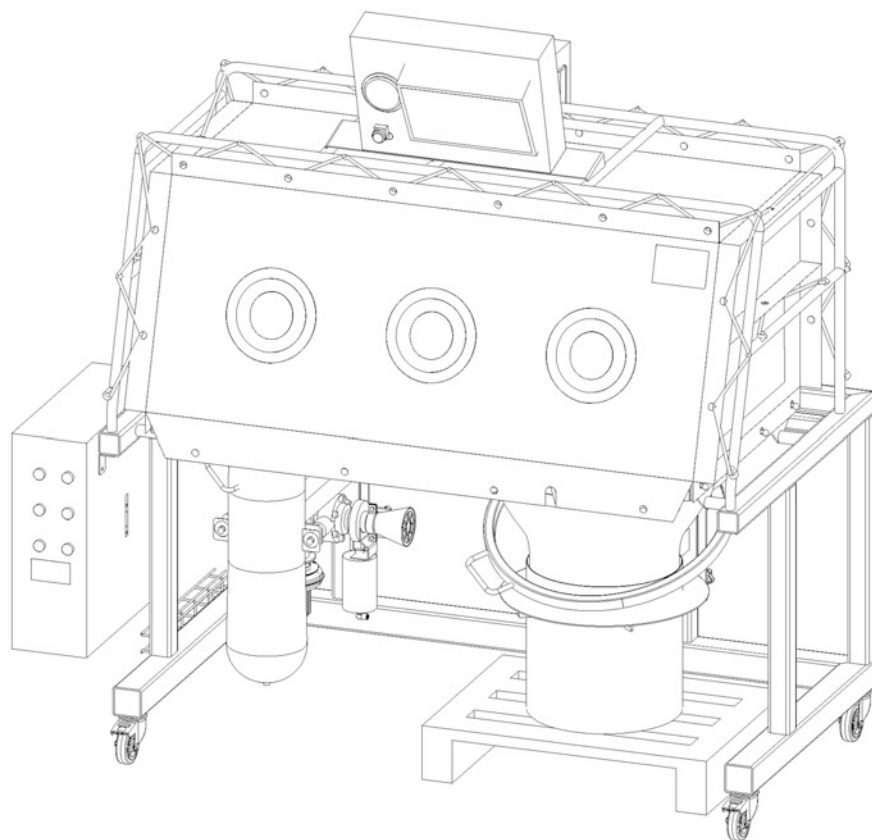


Fig. 2.2 Disposable foil isolator (Source HECHT Technologie GmbH)

working chamber or on the front window. The front door can be opened and closed by means of static or inflatable gaskets. If the isolator or glove box is openable, gas springs hold the window in open state in the safe upper limit position. Opening the doors should be controlled, by means of a lockable pneumatic switch, or managed with a locking cylinder. Isolators for the working with very toxic substances have no doors but windows, which are completely sealed.

The isolator is made mostly with a sloped floor to the drain and has a good visibility in the drain area. To clean the chamber, manual spray guns with a hose or fixed stainless steel piping with spray balls are provided.

Through safe replaceable HEPA filter systems (see [Sect. 4.1](#)), the supply air is taken from the installation room. The flow inside the working chamber is turbulent. The exhaust air is, based on a risk analysis, mostly double filtered and blown in an exhaust system. The filters can be designed as filter cartridges. For the safe exchange, the contaminated filter can be pushed with a second filter within a tube in the direction of the containment. The contaminated filter falls into the

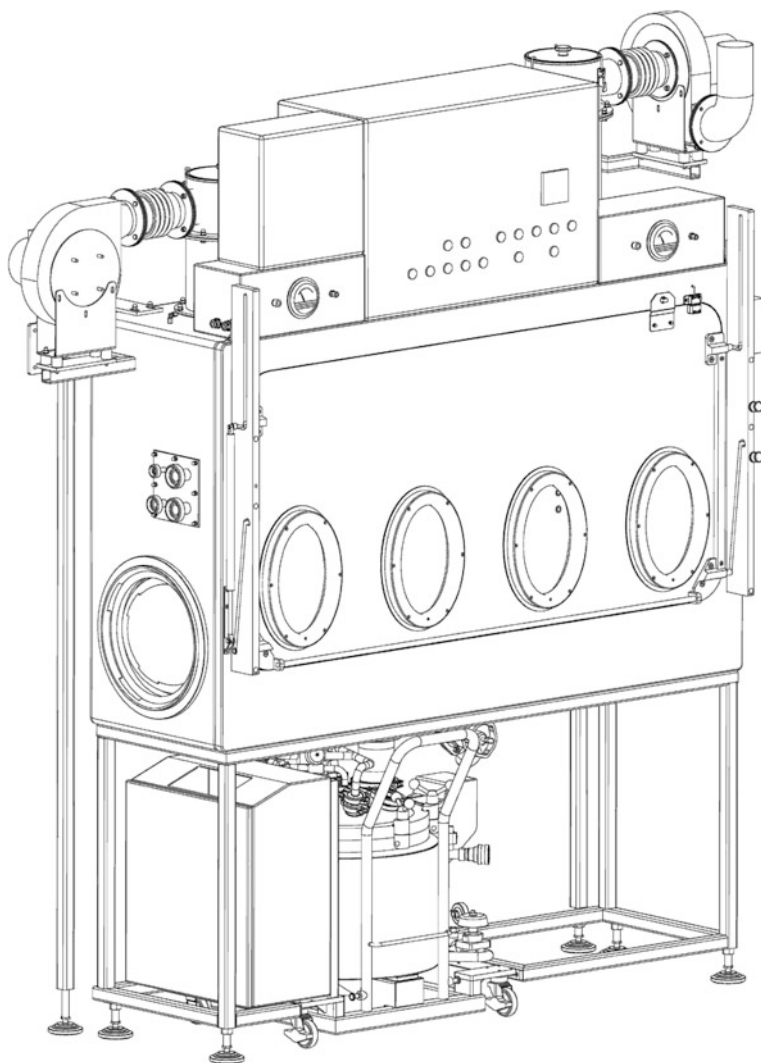


Fig. 2.3 Isolator for the production of highly active ingredients (*Source* SKAN AG)

containment, where it can be packed and removed. This system is called “push–push” filter system (see [Sect. 4.1](#)). Another technical possibility for a fast and safe filter exchange is easily replaceable filter cartridge systems like the so-called “FiPa” (see [Sect. 4.4](#)).

The air exchange in the working chamber takes place with the inlet air fan running on constant speed. A speed-controlled fan pulls the air from the isolator chamber to the exhaust and thus controls the working chamber differential pressure to the environment. In an emergency case like a glove rupture, the exhaust fan set

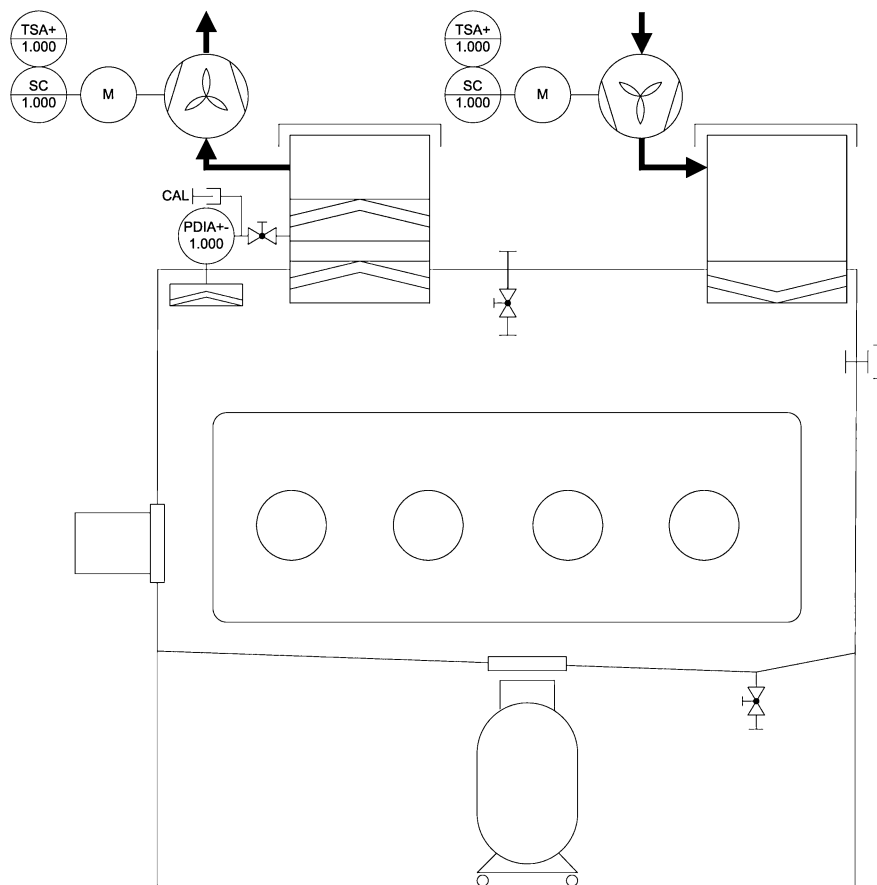


Fig. 2.4 Schematic of the air management and instrumentation

point goes up for personal safety, until the airspeed reaches the target from ISO 14644-7 [Sect. 9.2](#) of 0.5 m/s through the open diameter of the glove flange. The separation efficiency of the exhaust filter must be preserved. Optional charcoal filters can be used, depending on the material processed in the containment.

To perform a pressure hold test, the inlet and exhaust ducting of the isolator are pressure tight closed with blank covers or flaps. The measurement can be performed manually or fully automated as a pressure drop test.

The few control and regulating tasks can be completed by relays and pneumatic controls, electronic controls and small industrial controls are commonly used. Most sufficient are local control buttons, status lights, and alarm signaling lamps. Any malfunction must be highlighted to the affected operator immediately ([Fig. 2.4](#)).

For a partial production process as described in [Sect. 2.1](#), the different isolators can be arranged in a way, that the product to be processed follows the gravity

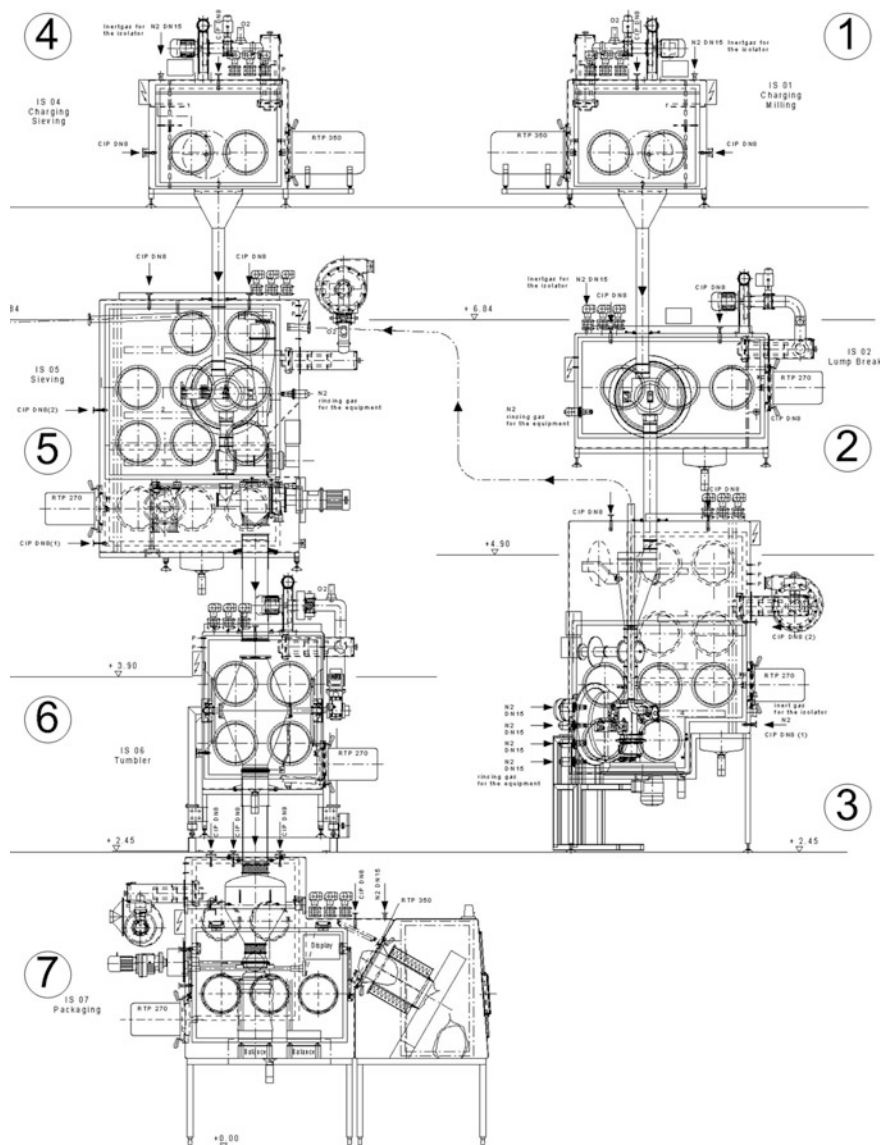


Fig. 2.5 Multistorey powder processing plant in isolator technology (Source SKAN AG)

(Fig. 2.5). The raw product comes via RTP container and is charged from top of the plant into the charging isolator (Fig. 2.5(1)). After passing the lump breaker (Fig. 2.5(2)) into the mill in the milling isolator (Fig. 2.5(3)), the product is transferred into the sifter (Fig. 2.5(4)). The micronized product is proceeding into the packing isolator Fig. 2.5(6)), while the overspill is reprocessed in the sieve.

The packed product will be discharged for example into a PE endless liner, closed with an adequate welding device.

Some applications in the pharmaceutical industry which are in many cases related to organic solvents or fine dusty powders require an explosion proof design of the containment.

Therefore, the process owner is required to prepare as part of his risk assessment an explosion protection document and classify where hazardous explosive atmosphere can occur.

The guidance on assessing the extent of the explosion hazard is given in the European “ATEX workplace directive 1999/92/EG” or in the American NFPA 497 Standard and API 500 as well as according to their adaptation by other areas gas zones is given in the current edition of IEC 60079.10. For hazardous dusts, the guiding standard is IEC 61421.10.

This European directive lays down basic safety requirements which the process owner has to implement. These include:

- Prevent or reduce the generation of explosive atmospheres (primary explosion protection)
- Avoidance of ignition sources (secondary explosion protection)
- Limiting the impact of a possible explosion to an acceptable level (tertiary or constructive measures)

Containments in which are organic solvents handled are usually defined with “Zone 1, temperature class T3 or T4”. Containments with dusty atmosphere are commonly defined Zone 21 with the maximum allowed surface temperature.

According to the results of the risk analysis, the isolator and its surrounding area is separated into different zones. The largest zone is mostly the surrounding room followed by an area close around the containment chamber. The inside of the containment itself and the ducting into and out of the containment are the other areas of interest. The intake air section of the chamber is normally of low risk due to high amount of fresh air flushing into the chamber. The chamber itself needs to be checked in the different operation modes of the air handling system and the different operator or process steps inside, including cleaning procedures afterward. The exhaust system is, in most cases, the same classification as the chamber itself.

If this analysis finds any hazardous areas, the first thing is trying to lower the risk by reducing the usage of the dangerous material. The second method is to lower the classification with a higher air exchange rate or the flooding with nitrogen inside the chamber or in the surrounding area. For powder processing equipment, the design of the flow path can be optimized to avoid dust in the surrounding area.

Explosion protection is a cost factor in every project and needs therefore a precise definition during the pre-design phase to avoid additional cost and time delays during the project design and construction phases.

2.1.3 Negative Pressure Glove Box for Pharmaceutical Applications

The application possibilities for negative pressure glove boxes are various. In the laboratory, they are used for the safe handling of toxic and more active powdery substances (Fig. 2.6). Typical activities are weighing and sample acquisition, assembly of small components, and product transfer.

The illuminated stainless steel interior is easy to clean and build with static-sealed windows and glove ports. The chamber is placed on a tube frame and the control technology is arranged behind the work area. For weighing in the range of milligrams, solid chamber housing and a vibration-free design of the fan drive is necessary. A scale with protective cover against air flow is recommended.

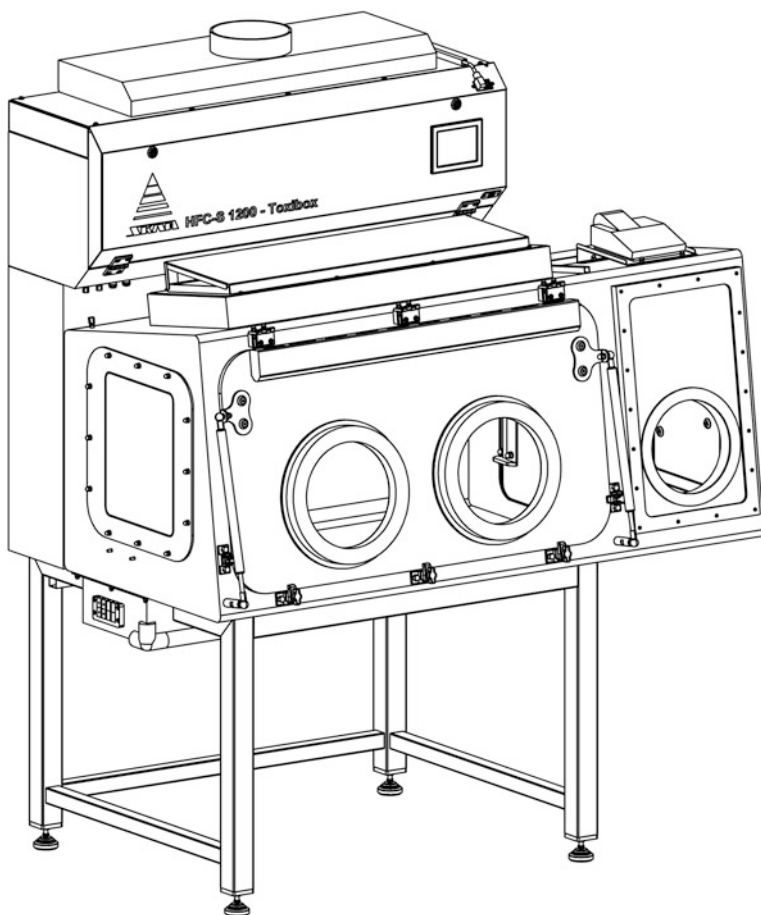


Fig. 2.6 Easy to clean personal protection glove box (Source SKAN AG)

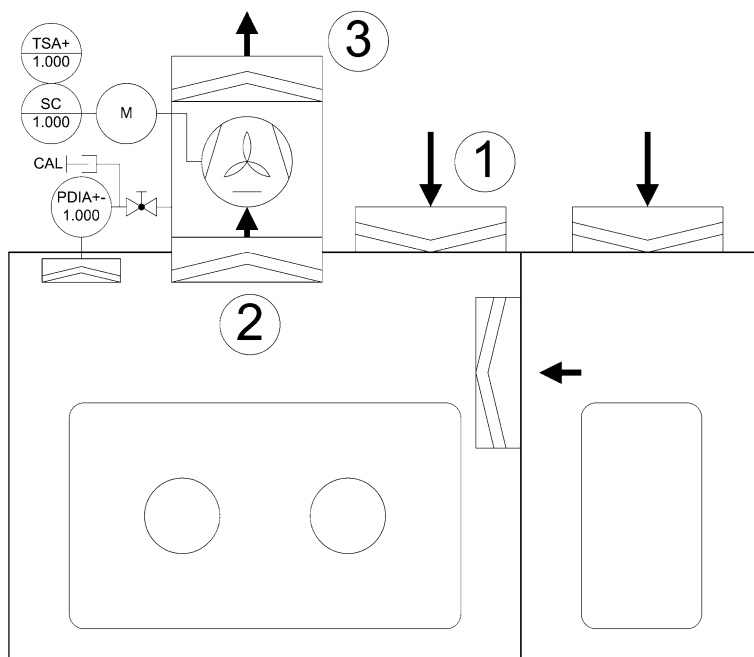


Fig. 2.7 Schematic of the air flow and instrumentation

The supply air from the room is filtered through the HEPA H14 filter in the isolator (Fig. 2.7(1)) and is sucked through with the negative pressure created by the exhaust fan. The working chamber has turbulent flow and reaches the clean room Class B (particle) at rest. The negative pressure is about -30 Pa, to ensure the operator safety from escaping dusts. The air from the containment chamber is sucked through a safe change filter system (Fig. 2.7(2)) located in the back wall and protected by a stainless steel sheet from not intended damages. The safe change filter can be changed by a bag out process. On the aluminum filter frame, a PE foil is tightly attached. The foil has rubber side bolster which serves as gasket for the filter. If the filter has to be changed, the metal sheet is removed from the filter and the filter is covered by the PE foil. Meanwhile, the exhaust air fan is holding up the negative pressure in the isolator. The covered filter can be removed from the isolator after a successful cleaning procedure.

A second HEPA filter (Fig. 2.7(3)) is installed in line in the air handling system of the isolator. Both HEPA filters can be leak tested in place. Behind the second HEPA filter, the air is returned to the room or displaced in the exhaust air system of the building.

An active carbon filter unit can be placed on top of the filter fan unit and allows the adsorption of volatile, gaseous, and bad smelling substances. Due to the slow flow, an optimal dwell time of the filtered, gaseous charged air is achieved and therefore a good retention effect can be observed. In addition, a solvent sensor can

be placed on the active carbon filter unit for the detection of a filter over load with solvents and flammable gases.

The airlock of the glove box is connected with a HEPA filter to the working chamber and is therefore also under negative pressure. Other transfer systems like RTP or split butterfly valve can be integrated.

The isolator usually has a simple microprocessor control for the pressure setting with alarm limits and a display of the working chamber pressure. Hour meter and filter differential pressure gauges are advantageous for the planning of maintenance cycles. For low risk weighing applications which are commonly performed in this isolator type, the doors and locks are not monitored. An SOP must be established to achieve all necessary safety features.

A spray gun is typically used for the cleaning of the working chamber and the airlock. A floor drain with a valve allows the safe disposal of liquid waste. Alternatively to the use of the spray gun to avoid liquid waste, cleaning cloths soaked with alcohol can be used.

2.1.4 Blister Machine Isolator

The isolator concept for a blister machine starts with a balcony construction of the blister machine. In this way, the isolator can be kept small. The isolator only protects those areas of the blister machine, in which open tablets or capsules are handled. The isolator is divided in the loading section (Fig. 2.7b(b)), where the tablets or capsules are coming from an intermediary bin (Fig. 2.7a(1)) via an RTP (Fig. 2.7a(2)) or a split butterfly valve to the hopper. During the transfer, it is important to ensure that the hopper is not flowing over. This can be done by a PE liner attached on the RTP (Fig. 2.7a(3)). The hopper is the area in the isolator, where most of the dust is created by the vibration of the tablets.

The second part of the isolator (Fig. 2.7b(a)) encloses the blister process, the area where the tablets or capsules are transferred into the cavities of the plastic foil. After thermoforming the plastic film, the foil with the formed cavities will pass the mouse hole on the bottom of the second isolator part. The whole isolator is in slight negative pressure to avoid the drag out of the hazardous dust. The mouse holes are protected by a curtain of compressed air. The web guiding rail in the bottom of the isolator is divided into two parts to facilitate the dismantling and the cleaning in the closed isolator.

After being filled, the web is passing the tunnel with the inspection camera. The camera is mounted outside the isolator using a window to control the blister. Immediately behind the camera tunnel, the web is passing the second mouse hole and is immediately sealed with the covering foil in the sealing station. From that point, the process is no longer considered to be hazardous. All further steps of the blister process are performed in the production environment.

The ventilation system of the isolator uses two push-push filters to bring fresh air in and to remove the dusty air from the isolator. The air inlet is in the blister

Fig. 2.7a PE liner attached on an RTP

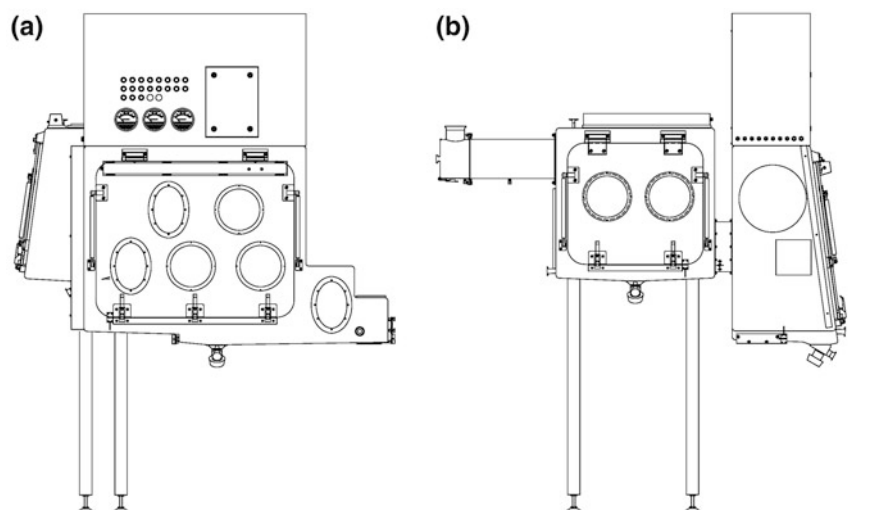
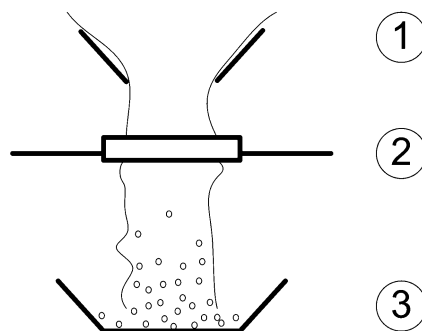


Fig. 2.7b Isolator on a balcony type blister machine (Source SKAN AG)

isolator, the area with less dust exposition, while the outlet air filter is located in the loading section. In this way, a constant flow from the blister isolator to the loading section is provided. In the air balance, the two mouse holes should be considered too.

Operating the blister machine in the containment, there are two glove ports in the loading isolator and five glove ports in the front screen of the second isolator part, which allow access of the operator to all surfaces in the isolator. The glove port locations were determined in a mock up study. Both screens are made from 15 mm safety glass and sealed statically to the isolator. For maintenance and drying purposes, both doors can be opened completely and are hold in open position by gas dampers. A RTP 270 is placed on the left side wall of the blister isolator to transfer tools and change parts during operation in a contained way.

During cleaning, all openings to the environment such as filters and mouse holes are closed; the cleaning process is performed in the closed containment before the isolator and the machine parts are not visually clean. Dry cleaning with the vacuum cleaner removes the major portion of the accumulated dust. The vacuum cleaner is attached to the isolator with a Banjo split ball valve. This valve allows disconnecting the vacuum cleaner without carrying out hazardous dust to the environment. In a second step, the WIP system with spray balls from the bottom and from the ceiling washes both isolator sections with an adequate wash program. The waste water is drained through a bottom seat valve into the waste water collection tank and afterward discarded. When the isolator and the encapsulated machine parts are visually clean, the isolator can be opened and the drying is done manually with wipes.

2.1.5 Isolation of Tablet Manufacturing of High Active Pharmaceutical Ingredients

Nowadays tablet presses are highly self-contained and washable. In an intermediary bin granulate comes on top of the tablet press and is docked with an RTP via a connecting glove box or with a split butterfly valve.

After the tablet press, the tablets go through a de-duster, which is also self-contained. The isolator for the metal check (Fig. 2.7c(1)) and the sampling (Fig. 2.7c(2)) is an isolator with three compartments. The third compartment (Fig. 2.7c(3)) is prepared to hold an automatic tablet testing device. In the left compartment is the metal check. Behind the metal check, the controlled tablets fall in two bins, which are outside the isolator attached with an RTP 190 to the bottom of the containment. The beta RTP is mounted on a PE in liner, which is in an intermediary bin. In this way, two bins can be filled with tablets before the operator has to change them. Immediately behind the metal check is a dividing hose, which allows the bad tablets and the samples to be taken out of the produced tablets.

The isolator is operated by nine glove ports, where two of them are mounted on the left side, four on the main screen, two on the right side, and one on the right side in the floor of the second compartment for taking the samples out. All glove port locations were determined in a mock up study.

The air handling is turbulent, the inlet air as well as the outlet air is filtered through H13 push-push filter in stainless steel housing. All filters are controlled by a pressure gauge. The control system is a relay control with optical and acoustical failure indication.

The floor of the isolator is sloped to the drain, which is a manually operated bottom seat valve. The cleaning is done with two spray wands connected to the deionized water supply.

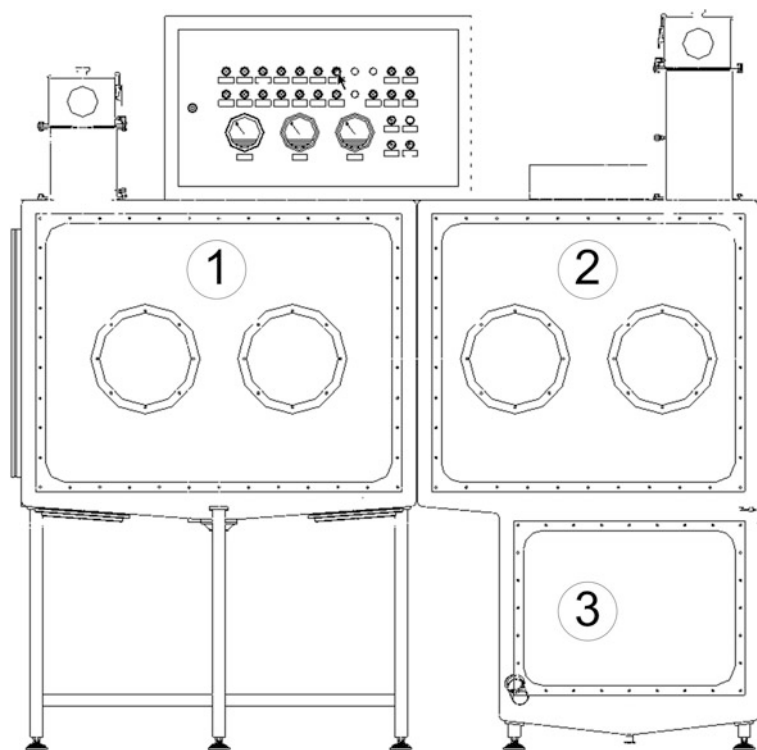


Fig. 2.7c Isolator for metal check and tablet sampling (Source SKAN AG)

2.1.6 Bottle Filling Line for High Active Tablets

The bottle filling line consists of several compartments, which are either with or without isolation. The bottle filling line is built up in three different rooms. In the first room, the empty bottles are inserted and if there are plastic bottles used, they are put in a bottle up setter, if glass bottles are in use; a safe pack turner is used to blow the bottles with clean compressed air. From this room, the bottles are moved on a belt through a mouse hole to the second room. In which they will be filled with the tablets and closed. Three or four compartments are installed in the second room, depending on the type of final packaging of the tablets. After outside washing and drying the bottles leave the second room to enter the third room, where labeling and packaging is done.

The first machine in the second room is the tablet counter (Fig. 2.7d(1)). The tablets are transferred to the tablet counter in an intermediate bin on top of the counter isolator. The bin holds an in liner on which an RTP 190 Beta is attached. The Beta flange is mounted on the Alfa flange, so that the tablets can be transferred. The tablets are in a PE in liner, which is closed with a tie. After having

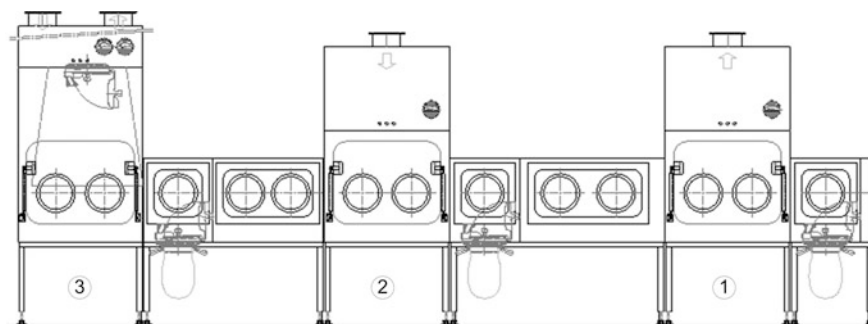


Fig. 2.7d Isolator for bottle filling line for high active tablets

attached the in liner to the RTP and the door is opened and a PE funnel is docked on the RTP, which guides the tablets to the hopper. Now the PE in liner can be opened, and the tablets are gliding into the hopper. The tablets are filled into the bottles. If the bottles are correctly filled, which is verified by check weighing, the bottles are transported to the next compartment, if not, bottles are eliminated from the line through an RTP port 190 into a plastic bag. In this isolator part of the filling line the most dust from the tablets is created. Operating the counter isolator, there are two glove ports in the front screen, which allow access of the operator to all surfaces in the isolator. The glove port locations were determined in a mock up study. The front screen and the side window are made from 12 mm safety glass. The front screen is hinged and can be opened for cleaning and maintenance purposes to upside, being hold by gas dampers in the open position. The window is sealed statically to the isolator.

If required, the second isolator compartment is a cottoner (Fig. 2.7d(2)), in which a cotton plug is inserted into the filled bottle. The cotton plug comes from outside the cottoner isolator via a small mouse hole into the cottoner isolator. If the cotton plug is correctly placed, the bottle is transported to the next compartment on the transport belt, if not; the bottle falls through an RTP into a plastic bag. The front screen of the cottoner isolator is divided into an open able part and a static part. In each part is an oval glove port to operate the cottoner.

In the next isolator compartment is a capper (Fig. 2.7d(3)), which is automatically screwing caps on the bottles. The screw caps are coming from outside via a mouse hole in the isolator. If the bottle is tightly closed, the bottle moves on to the outside washing machine, if not, it is removed from the belt through an RTP in a plastic bag. All compartments are connected with a belt, which is covered by a hermetically closed tunnel. In the tunnel are the 190 removal RTP's for the rejects. The capper isolator has the same front screen as the counter isolator with two glove ports. A third glove port is mounted in the left side wall. An RTP 270 is placed on the right side wall to transfer tools and change parts during operation in a contained way.

Due to the fact, that the most dust is created in the counter isolator, the airflow is directed to this containment. The second area, which has to be considered as critical for the process, is the outside washing machine. There is a high content of moisture, which should not come in contact with the open tablet bottles. The second air outlet is in the washing machine, so airflow from the capper to the washing machine and to the counter isolator can be achieved. The makeup air is filtered through a H13 push push safe change filter (see [Sect. 4.1](#)), the two air outlets are protected by two push push filter cartridges in series. During operation, when the mouse holes are open, also the air influx from the mouse holes has to be considered in the pressure balance of the system. The exhaust air is sucked into a dedicated air handling system.

During the cleaning process, all openings to the environment such as filters and mouse holes are closed. Each mouse hole cover is controlled by a proximity switch. Dry cleaning with the vacuum cleaner removes the major portion of the accumulated dust. The vacuum cleaner is attached to the isolator with a Banjo split ball valve. This valve allows disconnecting the vacuum cleaner without carrying out hazardous dust to the environment. In a second step, the WIP system with spray balls from the bottom and from the ceiling washes both isolator sections with an adequate wash program. The waste water is drained through a bottom seat valve into the waste water collection tank and afterwards discarded. When the isolator and the encapsulated machine parts are visually clean, the isolator can be opened and the drying is done manually with wipes.

2.1.7 Glove Box with Pure Gas Atmosphere (Inert Gas)

To protect sensitive substances, products or production processes from the influence of oxygen, moisture and other ingredients, controlled inert atmosphere glove boxes are used ([Fig. 2.8](#)) [3]. Inside the box is a high-purity nitrogen or argon atmosphere maintained. For special uses other gases (e.g., helium or sulfur hexafluoride SF₆) or gas mixtures (e.g., with an admixture of carbon dioxide) are used.

The attainable residual concentrations of contaminants are in operation continuously below 1 ppm. Glove boxes with high-purity inert gas are mainly used in the following areas:

- Basic chemical research (organometallic, catalysis, materials science)
- Semiconductor research and production (including organic semiconductors such as OLEDs, but also, for example encapsulation steps of conventional semiconductors and LCD displays)
- Battery research and production (Li-Ion or Li-Ion, Li coin cells)
- Welding (laser welding of parts made of titanium under argon atmosphere in medical technology: pacemakers, implantable hearing aids, application in the aircraft industry: e.g., for turbine parts made of titanium)

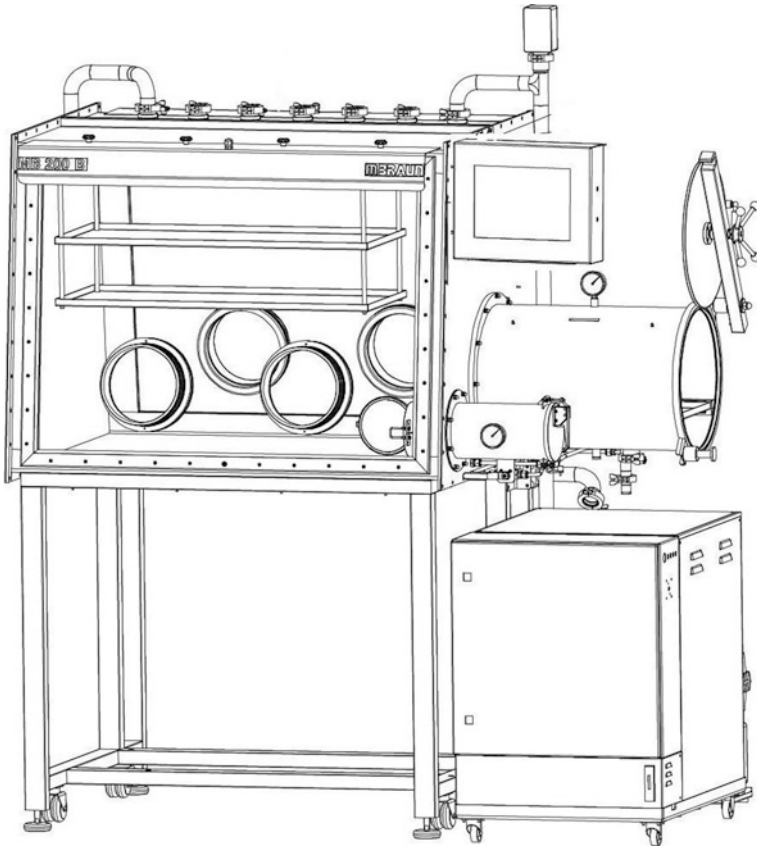


Fig. 2.8 Simple glove box with gas purification unit (Source MBRAUN Inertgas-Systeme GmbH)

- HID lamps manufacturing (xenon lights, sodium vapor lamps)
- Nuclear engineering, medical and pharmaceutical technology (e.g., for filling operations from the air decomposed or spontaneously combustible materials themselves)

The systems (Fig. 2.9) are used in universities, research institutes, and development departments of industrial firms for research and development to prototype stage and in industrial manufacturing plants. The glove boxes are generally made of stainless steel and are equipped with an adequate number of glove ports. There is a wide range of different designs, ranging from small boxes for the laboratory with two glove ports, to modular systems with customer specific layouts for the integration of complete customized processes. The systems are equipped with gas cleaning units with integrated blowers, where the gas continuously circulates and is cleaned from impurities.

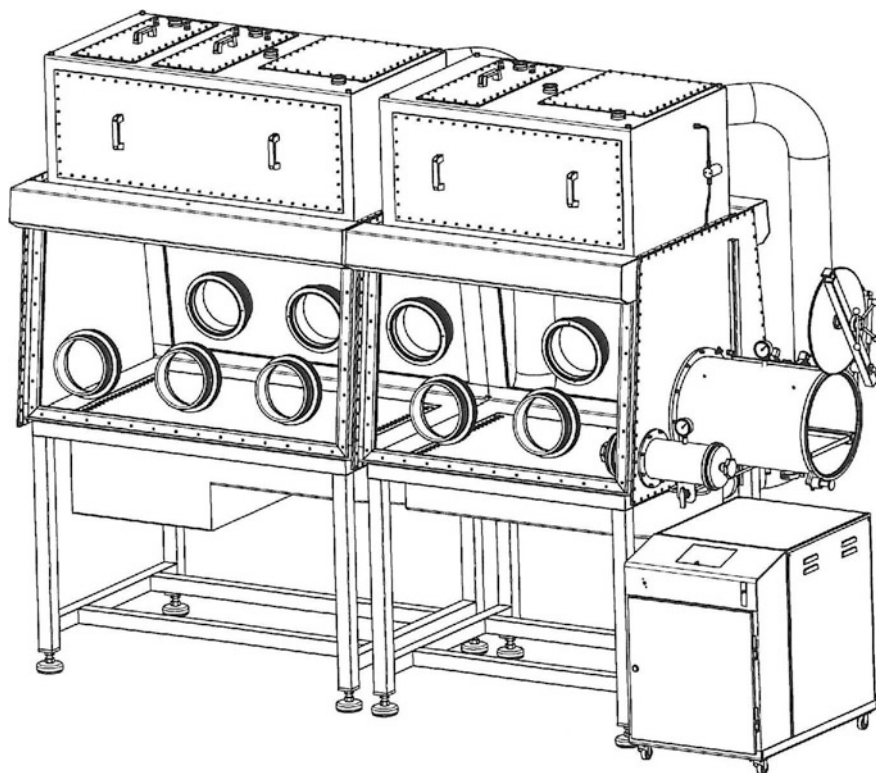


Fig. 2.9 Glove box with pure gas cleaning unit and laminar flow system (Source MBRAUN Inertgas-Systeme GmbH)

Special designs also offer the possibility of producing a directed flow in the box (laminar flow) to ensure standardized clean room classes in the work area. To achieve safe concentrations below 1 ppm, the assembling needs especially low leak rates of all components and connection flanges. The integral leak rate of the boxes is typically less than 0.05 vol. %/h (according to ISO 10648-2 Class 1). The gas circuit design comes from the vacuum technology with leak rates $< 1 \cdot 10^{-6}$ mbar l/s. The materials will be selected with the performance target of a very low outgassing and gas permeability. For example, embodiments of butyl rubber with a low permeation rate for oxygen and moisture will be used. For the introduction and the removal of goods and materials, the systems are fitted with one or more vacuum locks.

The contaminant concentration of the atmosphere is continuously monitored in operation by appropriate sensors in the circulation line. These sensors are usually at least sensors for traces of oxygen and moisture (Fig. 2.11). After installing the system, the required amount of relatively pure gas is at about 10 times the box volume. By flushing with large volumes, the gas in a closed system is continuously

circulated through a gas cleaning unit with built-in filters or reactors. In the filters are mainly molecular sieves used based on zeolites for the removal of water vapor and various hydrocarbons as well as special catalysts. The removal of oxygen occurs by copper catalysts which consist of highly dispersed evenly spread copper on a mineral carrier material. At room temperature, the oxygen is removed by chemical reaction with the copper during copper oxide is formed from the gas mixture.

Depending on the expected impurities, there are also filters with activated carbon and impregnated, for example, to remove acidic gases. The removal of nitrogen traces can be bound in reactors to metallic titanium at high temperatures ($>800\text{ }^{\circ}\text{C}$).

Depending on the design of these filters, they can be operated for several days up to weeks, until the capacity is depleted. By regeneration, usually a combined heating, washing and evacuation process, the gases are desorbed again. The regeneration is generally carried out in the system itself; thereby normally the full capacity is restored, so that the filter can be operated for years with the same loading. During the process of regeneration the gas flow is not interrupting the cleaning of the box atmosphere, except very simple laboratory boxes, the filters are designed to be installed double to keep always one filter in operation and another in regeneration or in reserve.

The working pressure in the boxes can be set usually within the limits of $\pm 1.000\text{ Pa}$ (condition for comfortable work with the gloves is usually $\pm 500\text{ Pa}$). To control the pressure fluctuations during temperature changes or work with the gloves, fresh gas is added to increase the pressure or pumped out with a vacuum pump to lower the chamber pressure. Heat sources in the box can be compensated with an additional cooling coil, which is supplied by a cooling unit (Fig. 2.10).

The systems are usually controlled with standard industrial PLCs, for simple devices also unique micro-controller-based systems are used. The interaction with the user to view or change the operating parameters and statuses are via a pressure-sensitive control and display interface. This allows selecting and monitoring the different modes of operation (circulation, regeneration, operation of locks). With the integration of production equipment or machinery in the glove boxes (Fig. 2.11), communications between the individual systems are usually performed via bus systems (e.g., Profibus) or digital status and control signals. For the execution of complex production processes all the possible interactions between the process and the inert gas system have to be considered (e.g., response to unwanted impurities of the atmosphere, contamination from the process equipment, and protection of the system against manual intervention).

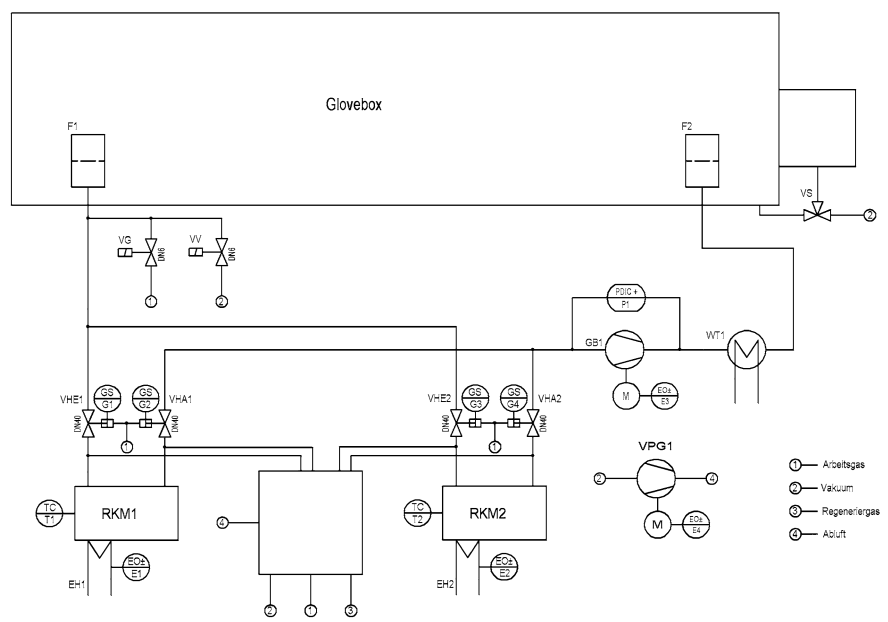


Fig. 2.10 Simplified flowchart of an inert gas glove box with a lock and gas purification [3] (Source MBRAUN Inertgas-Systeme GmbH)

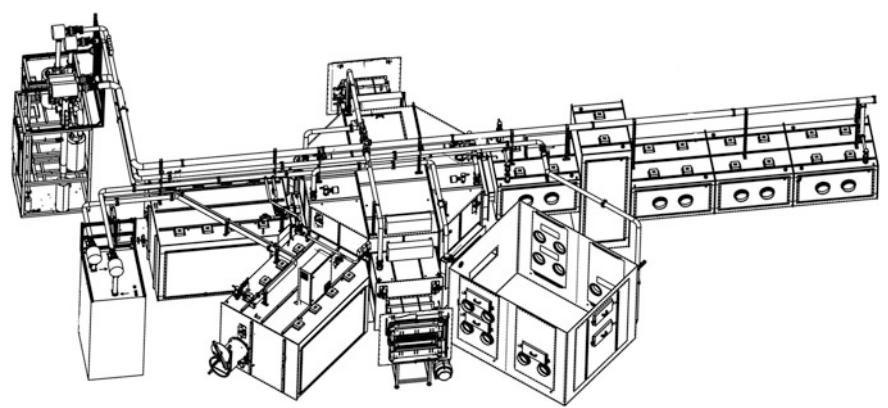


Fig. 2.11 Production line for organic light-emitting diodes (OLED) with central robot box, process boxes and gas cleaning units (Source MBRAUN Inertgas-Systeme GmbH)

2.1.8 Hot Cell/Isolator for Aseptic Work with Radioactive Substances/Radiopharmaceuticals

For the manufacture, bottling and processing of radioactive medicinal (radio-pharmaceuticals) so-called “hot cells” are used to implement the protection against radiation. The corresponding GMP conditions must be met for the work and the relevant process steps. In particular for the production of radiopharmaceuticals, e.g., for use in the field of Positron - Emission Tomography - method (PET)) and other nuclear medicine applications in the diagnosis and treatment, the conditions of clean room class “A” standing in clean room class “C” are required.

The production of radiopharmaceuticals is partially automated in modules (synthesis modules-especially in the area of PET). Conventional radio-pharmaceuticals, however, are prepared manually or semi automatically. For filling and aseptic filling so-called “hot cells” are used (semi-or fully automatic modules) with unidirectional air flow.

For the radiation protection of alpha and β -emitters, sufficient shielding is in most cases polymethyl methacrylate (PMMA). For the use with high-energy emitters, a local shielding will additionally be installed inside the containment for the necessary radiation protection in the form of lead bricks (Fig. 2.12).

Fig. 2.12 Containment for the processing of radioactive substances in the nonpharmaceutical field (Source Isotope Technologies Dresden GmbH)



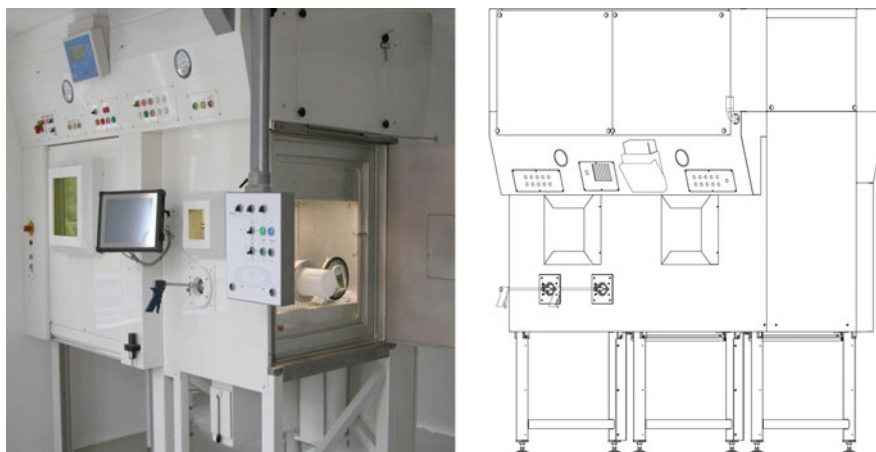


Fig. 2.13 “Hot cells” for the aseptic packaging of radio-pharmaceuticals (*Source* Isotope Technologies Dresden GmbH)

“Hot cells” (Fig. 2.13) are built from the elements described below: In a frame one or more boxes are made of stainless steel (cells). Around these cells, there is a specific shielding that is useful for the used radionuclide and its activity. For this shielding, lead is typically used in the form of lead bricks. For large cells concrete is used as a shielding. In the cells are integrated remote control elements, according to the necessary work steps. These are depending of the shielding thickness (100–150 mm lead) rigid manipulators (manipulator consisting of a ball joint, and a gripper with boot). For shields with a thickness of 150 mm of lead or concrete master slave manipulators are used (manipulator arm consisting of the inside (warm) and outside (cold), a lead through, grabs and a booting).

On the front side is, equivalent with the shielding, an optics with a lead glass window. Light, media, tubes for nuclide, including for the coverage within the hot cell, are specially sealed flanges in the ceiling or the floor area, realized with the help of tight fittings. A mounting or cover as service opening is located at the front- and or backside, in the form of a door or a retractable shielding. These openings are sealed to the cell with PMMA or glass. All operating and control elements are located above the “hot cell,” integrated into the casing, which is fitted into the space on site.

The transfer of radioactive and nonradioactive materials is done preferably at ground level or on the side with a transfer lock. Therefore are locks in the form of other cells or double transfer locks provided, for example, rapid transfer port systems (see Sect. 6.3.1.). The entire execution, such as the arrangement of cells and lock systems, will be customer—and process-specific adapted according the physical and technical conditions.

For the production and use of radioactive drugs and the preparation of dosing and filling processes are “hot cells” used with the unidirectional air flow.

Therefore the fans are moving the air in the recirculation mode. In addition, the necessary negative pressure in the cell is created for working with radioactive substances. With filtered intake air—mostly from the installation room—and filtered exhaust air—often using activated charcoal as an additional filter step—the fixed air exchange rate is ensured by appropriate valve settings.

The “hot cell” is designed for the aseptic work with the help of semi-automated systems, automated systems or manipulators. The equipment in the field of “cell” technology, such as filling lines, opening and closing systems and measurement technology, is customer—and application specific and must be prepared for the special handling with corresponding manipulators. The processes are mostly operated with interchangeable modular systems. Necessary pressure and zoning classifications are based largely on the volatility of the processed substances and the risk to operators and to the environment from radioactive substances. Within the box, the process is executed by using semi-automated, automated systems, or gloves.

The “hot cell” separates product, process and operator during the entire process. It prevents the biological and radioactive contamination from the environment. The cleaning is done according to the arrangements generally as “clean in place” (CIP) for microbiology and special cleaning agents for the radioactive decontamination. The use of a H_2O_2 decontamination system (See [Sect. 8.1](#)), also as a mobile version, is possible but in this case an activated charcoal filter step cannot be integrated.

According to the spatial requirements, these systems are covered. Needed elements for operation, measurement and control devices are integrated in the front panel for simple accessibility and easy operation. The probes for the physical monitoring system such as particles, air velocity, dose rate and others are mounted on the “hot cell” for easy operation.

Technical devices inside the hot cell are operated by an independent control. All major system components and consumables are remotely exchangeable. Electric and pneumatic controls are inserted in the panels.

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