

# Handling of high potency drugs: process and containment

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## Abstract

Modern process plant design and the issue of containment will be discussed in this paper. This topic is particularly important when handling dangerous (or active) substances in powder form. The kinds of techniques presented are mainly applied in the pharmaceutical and nuclear industries.

This paper will examine issues in high potency powder containment, particularly the concepts of containment, permanent physical barriers between product and operator, negative pressure isolator containment to ensure safety in the event of glove malfunction or accidental door opening and isolator chamber cleaning systems. The various types of isolators, from a simple single chamber to more complex double chamber systems or special connection systems such as external boxes for material ingress/egress, will be described. Also the uses of isolators throughout an entire production plant will be discussed from dispensing operations, through reactor loading and centrifuge unloading, to final product unloading from the drier.

*Keywords:* containment, isolator, glove box, safety, industrial hygiene, pharmaceutical, nuclear.

## 1 Introduction

In the recent years, the Pharmaceutical Industry has developed new and more potent Active Ingredients, particularly in the field of cytotoxics for oncologic use. At the same time, companies are paying increased attention to problems of Safety, Industrial Hygiene and the Environment. As is well known, these kinds of problems can also bring undesired consequences many years after the production campaign. This usually requires companies to pay very high



reimbursements. Furthermore, the regulations force companies to use and apply the so called “Best Available Techniques” in order to obtain an acceptable level of protection for working people and for the environment. The sum of the factors mentioned above has driven increased attention to the technology of “Containment” of highly active powder.

## 2 Range of application

The range of application of the containment technology is very wide. Isolators were initially used mainly in nuclear applications and later in other branches of industry, such as: asbestos disposal, electronics, potent drug production and dispensing, sterile pharmaceuticals, biological research and analysis, medical and military. We will focus on those applications where the driving concept is the protection of operators and environment. Applications where the aim is to protect the product itself (i.e. sterile pharmaceuticals) from the external environment will be not discussed. Isolator technology is used when there is a risk of scattering of a dangerous powder or a liquid forming aerosol and when a manual operation is required. Powders are dangerous because they are easily transported by air depending on their density, particle size distribution, shape, electrostatic load and many other factors which are difficult to be known and managed. Typical situations that require the application of isolators are operations where the powder is to be transferred by means of a manual action. Some examples are listed below: transfer from a piece of equipment to a container and vice versa, transfer from one piece of equipment to another piece of equipment which cannot be permanently coupled, weighing, dispensing from a larger container to a smaller container, milling, delumping, sampling, dissolution of a dispensed powder in a liquid, research and development when small quantities are involved (i.e. reaction, filtering, drying, inoculum, analysis.....).

## 3 General safety issues

Each Company or Institute which has to face the problem of handling of a potent compound has to acquire data on the toxicity of the powder itself. This research can be very difficult and it normally requires a significant effort by industrial hygienists and occupational doctors. Suppose that the result of the above mentioned study is that the concentration of the potent powder in the environment has to be kept below few micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) to prevent operators from having adverse effects. In this case, the only available technology to achieve the very low concentration is by using isolators for containment. A special situation exists for research and development operations. In this area, scientists do not yet know the activity of the molecules that they are developing. For this reason, it is certainly advisable to use a higher level of containment to avoid unexpected problems.

Some additional reasons for applying isolator technology, we can say that these devices comply with generally accepted safety concepts (also incorporated by many laws) of containing a danger at the point where it originates (ab



origine). Furthermore, the excellent level of containment guaranteed by isolators allows the operator to not wear Personal Protection Equipment (PPE), normally very uncomfortable for active powders.

## 4 General isolator description

Isolators can be designed and constructed in many different ways with the addition of many possible accessories. This paper intends to present how the activities performed in the isolator influence the design of the isolator itself. A disadvantage of isolators is their high cost so each construction component or accessory must be justified by an operative need. This applies to production plants where the process is well known and costs have to be minimised. However, in the field of chemical and biological research it is better to have a more integrated piece of equipment in order to achieve more flexibility in the operation performed.

### 4.1 Containment enclosure

A simple representation of an isolator is shown in Figure 1. The enclosure which forms the barrier between the dangerous powder and the operator is composed of sheet metal, glass, rubber gloves and special doors. The tight seal between the pieces is the basic reason for the safety of the device. We identify such an isolator as a “passive” piece of equipment because it hasn’t the “active” ventilation explained below. A “passive” isolator has limitations, in fact, each material added to the process has to be introduced to the isolator at the beginning of the operation and everything must be cleaned before opening the door at the end of the work. A minimum accessory to improve the operability of the machine is a connection for a special container to deliver a dispensed material or to dispose of pieces of rubbish.

### 4.2 Isolator ventilation

In order to reinforce the safety provided by the physical barrier of the isolator itself, a ventilation system is often used to ensure a negative pressure inside the isolator chamber. Both the inlet air and the exhaust stream to the ventilator suction are properly filtered (with HEPA filters or cartridges). The differential pressure ( $\Delta P$ ) between the external environment and the working volume inside the isolator is very important to prevent leaks in the physical barrier. In fact, any possible leak through a crevice will be into the isolator, which prevents the spread of active powder. The negative pressure inside the isolator (typically -20/-100 Pa) is also important in case a glove breaks or during an accidental door opening.

### 4.3 Nitrogen padding

Similar to flammable liquid storage, the air ventilation through the isolator can be replaced with a nitrogen stream. This solution doesn’t jeopardise the negative pressure inside the isolator and the nitrogen consumption can also be reasonable.



Removing the oxygen from the working chamber allows the isolator to operate safely with potentially explosive powders. This action is strongly recommended when the dust explosion parameters are unknown.

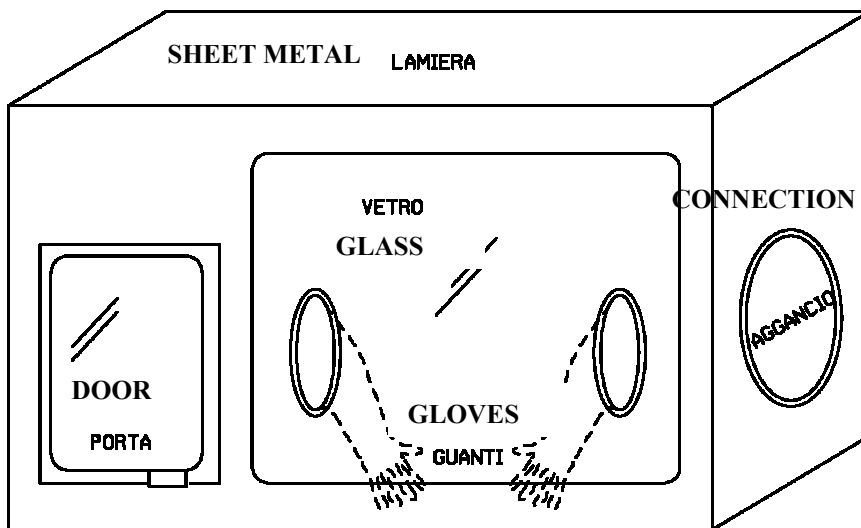


Figure 1: Isolator.

#### 4.4 Cleaning in place (CIP)

The isolator internal volume and anything within the isolator is potentially contaminated once the active powder is released. Starting from this point, each isolator door opening to the external environment must be preceded by a cleaning and decontamination process. Proper data on the powder solubility and inactivation must be determined first. For effectively performing cleaning operations, CIP skids are used. These systems are composed of a central distribution unit with tanks, pumps and, sometimes, heat exchangers. The cleaning liquid is introduced by means of spray balls and spray guns installed inside the isolator. Special attention must be paid to the liquor collection system which needs to be equipped with “dry link” valves.

### 5 Ingress/egress transfers

We have already stated that each transfer from (or towards) the internal volume of the isolator requires a door opening and cleaning each object which can be potentially contaminated. In order to avoid wasted time when the process needs to transport goods into the isolator, a Pass-Box can be used. This auxiliary chamber is connected to the main working chamber by means of a door and has a

very simple cleaning system. In fact, when the operator needs to open the external door to place the object inside the Pass-Box, he must be sure that no powder traces are left from the previous ingress step.

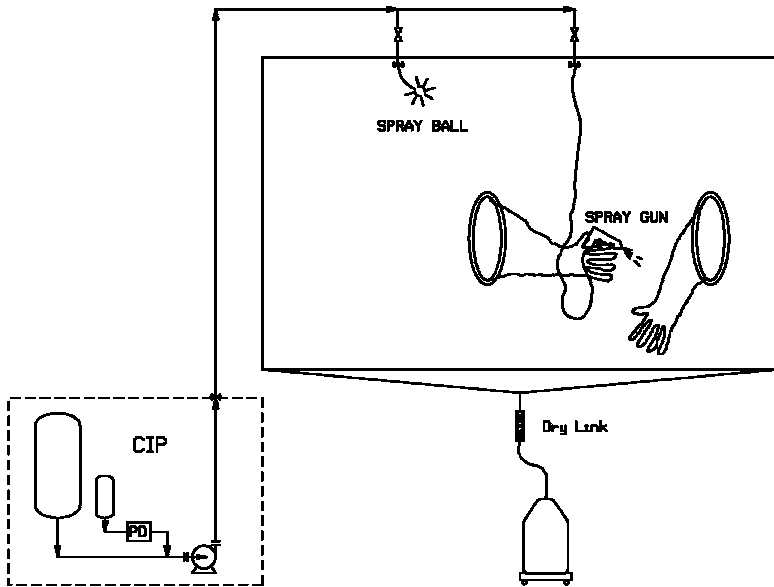


Figure 2: Cleaning in place system.

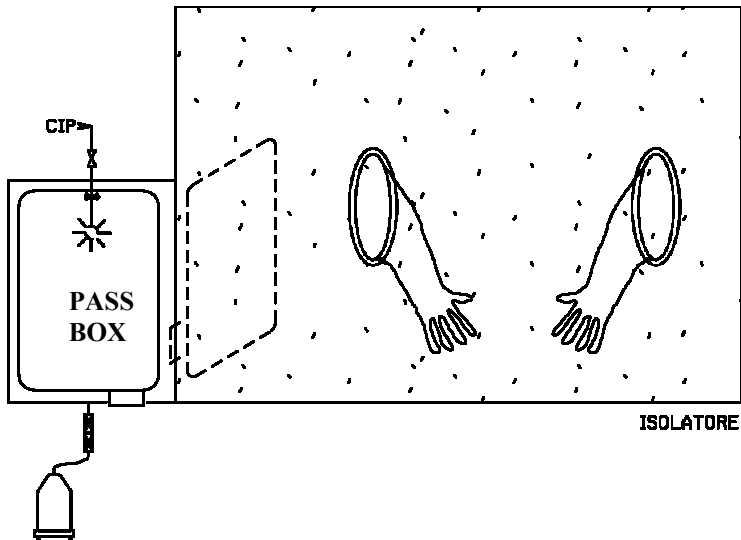


Figure 3: Single chamber isolator plus pass-box.

For processes which require frequent egress of objects that need to be reused (i.e. tools, excess reactants, small containers....) a Pass-Box as described above is not enough. The Pass-Box doesn't allow the operator to manipulate the object and, as a consequence, to decontaminate the pieces before exiting the auxiliary chamber. For this reason, a completely independent "pre-chamber" is installed especially for Dispensing Isolators or for Research Isolators. This can double the cost of the isolator but provides a larger and more flexible operation.

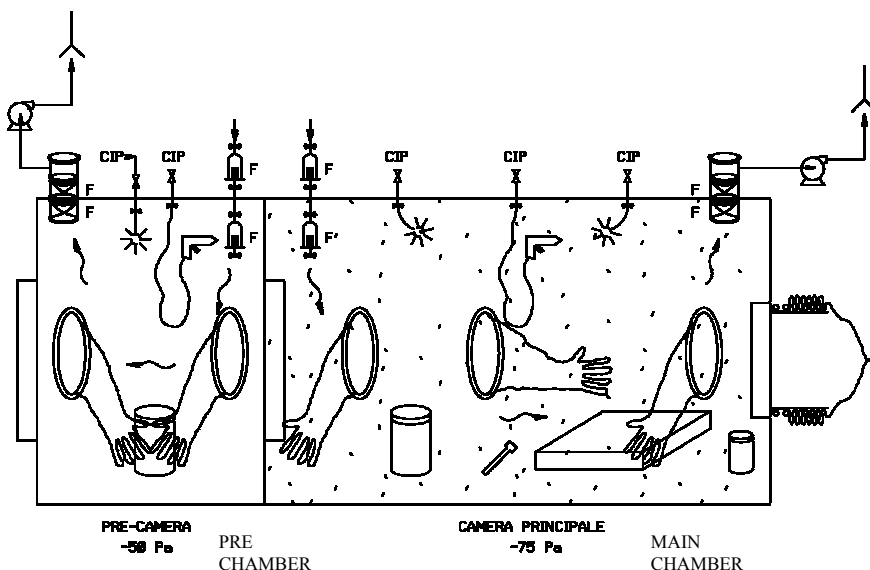


Figure 4: Dual chamber isolator.

## 6 Containers and connection systems

An effective method to speed up powder transfer operations is to utilise special containers with safe coupling systems to the isolator body. The traditional system of the two valves (see Figure 5) is not considered safe enough when processing an active compound. In fact, there are potentially contaminated surfaces which come in contact with the external space when the container is disconnected. There are patented systems (i.e. Twin-Valve<sup>®</sup> Vima) which clean and dry the dirty surfaces before uncoupling. Another commonly used device is the so called "split butterfly" valve which works on the principle of leaving "zero" volume between the two "half valves" (see Figure 6). Such systems are patented by: Glatt; Buck; Romaco-Zanchetta; Gea and other suppliers.

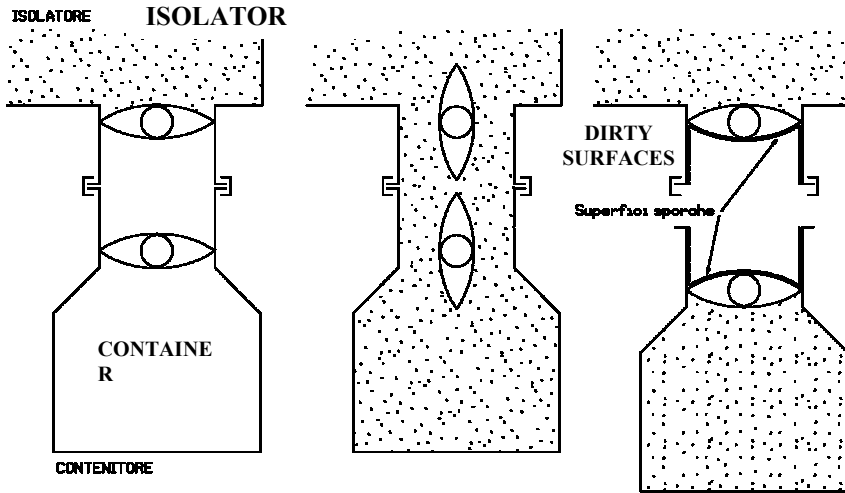


Figure 5: Container connected with two valves traditional system.

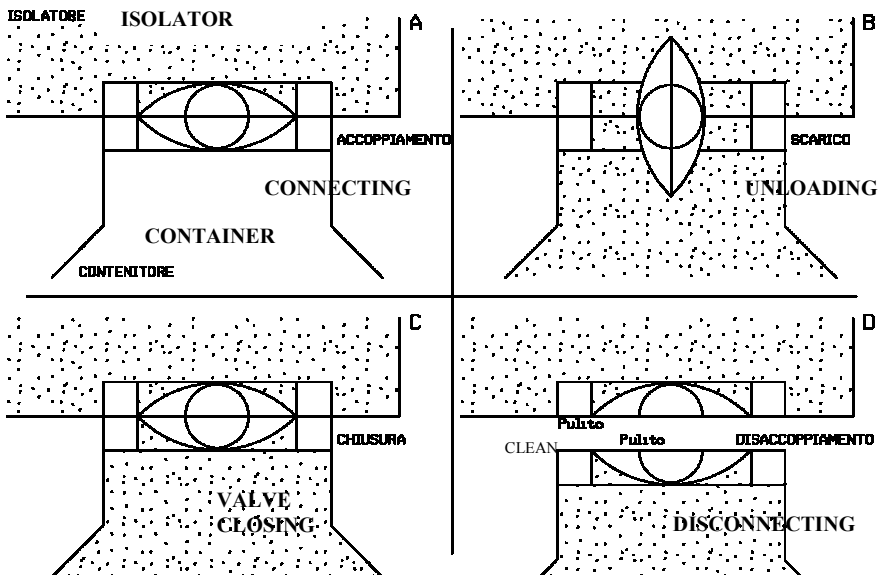


Figure 6: Container connected with split butterfly valves.

A system for coupling a container to an isolator body which ensure a very good level of containment is the Rapid Transport Port (RTP) device (i.e. DPTE<sup>®</sup> la Calhène). This system is sketched in Figure 7. This system is based on a dual circular door which ensures a hermetic closure among the two circular central parts (see nr. 2 and nr. 4 in Figure 7). The RTP system also ensures that it cannot be opened until it is perfectly coupled and, vice versa, it is impossible to disconnect the container until the door is completely closed.

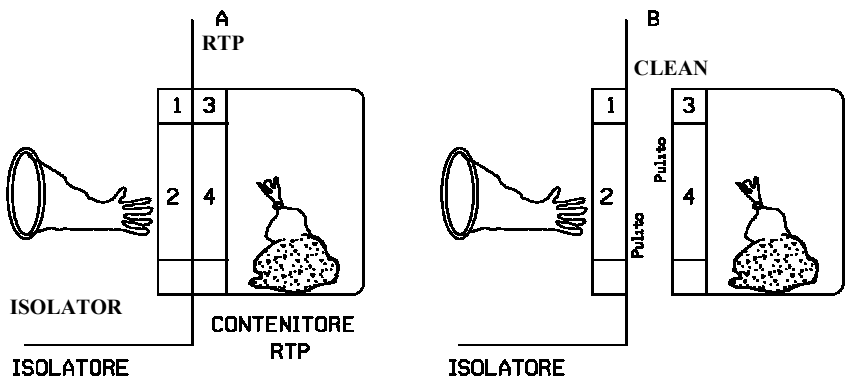


Figure 7: Container connected with a RTP system.

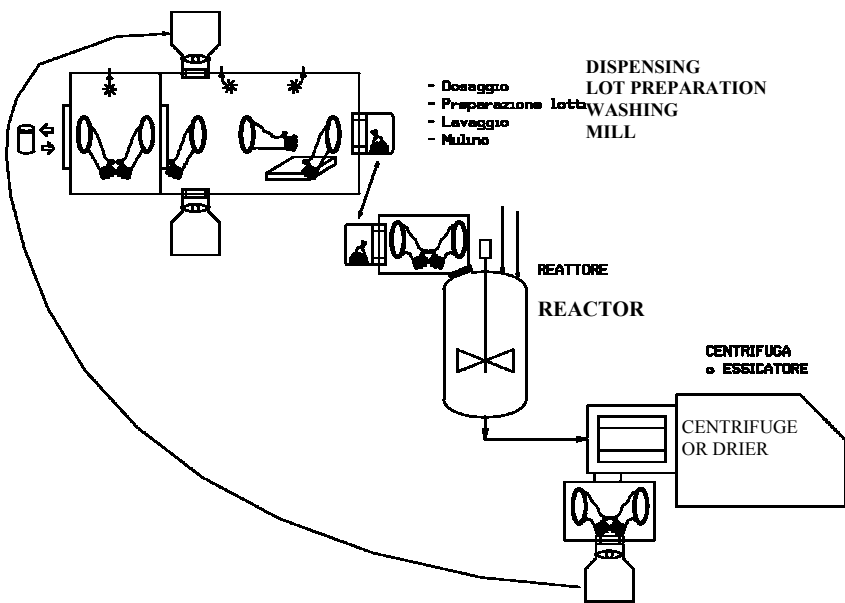


Figure 8: Process flow diagram of a plant for potent drugs production.



## 7 Production plant for active ingredients

For producing an active ingredient classified as a “potent drug”, all the plant must be designed considering the containment problems related to powder transfer. The example shown in Figure 8 represents three different situations.

- 1) Dispensing isolator, where the potent compound can be weighed, delumped, received, dispatched or placed into RTP containers after being dispensed.
- 2) Reactor loading isolator for safely loading dangerous powder into reactors (reactants, intermediate products, catalysts, etc.).
- 3) Centrifuge unloading isolator for unloading potent intermediate products or the final product to be dried. The same concept of the Centrifuge unloading isolator can also be applied to the drier unloading operation.

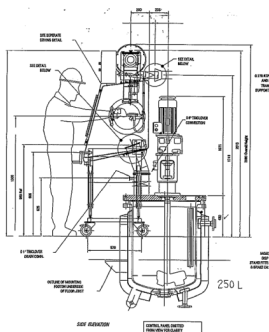


Figure 9: Reactor loading isolator.

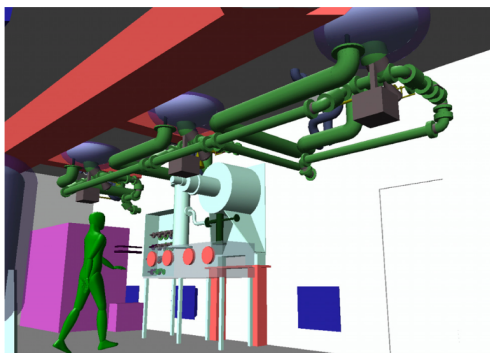


Figure 10: Centrifuge unloading isolator.

## 8 Conclusions

Containment and handling of potent powder is a difficult problem. Many technologies have been developed in recent years to safely and successfully handle these powders. An exhaustive study of several aspects like toxicity, material flow, production process, ergonomics, industrial hygiene and safety has to be performed. This has to be done also to avoid over-design of the system which can be very expensive. However, because of the increased need of safety and environment compliance, this topic is foreseen to increase significantly in the near future.

## References

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