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The Power of Together

WHAT ARE SOME HIDDEN RISKS ASSOCIATED WITH ISOLATORS?

WHITEPAPER SCHEDIO SA
NOVEMBER 2022

ABSTRACT

Pharmaceutical and fine chemical companies, sometimes underestimate or do not consider certain risk factors, when it comes to glove boxes/isolators usage while working with hazardous materials.

Safety should be a number one priority when operating machinery. This involves putting the operator's safety at the highest level and minimizing injury risk for the operator and decreasing chances of a poorly developed or non-useable product.

It's time to uncover the hidden risks associated with isolators and discover the Schedio approach of putting safety first.

CONTENT

THE IMPORTANCE OF ISOLATORS

Isolators are used to protect the operator from hazardous materials/products being handled. They also help protect the product itself, whether it be flammable or when it tends to oxidize by providing a controlled environment.

During production of products or ingredients for pharmaceutical and fine chemical companies, isolators maintain containment of each process. They are important for both operator and product because they help keep the operator and the environment separated from the active pharmaceutical ingredient (API).

With well designed isolators, operators are able to work productively and still efficiently while the isolators eliminate contamination from environments as they keep not only the operator safe, but the API safe as well. Whenever manufacturing isolators, assessments need to be created to understand what process needs to be contained and how.

The right containment level has to be determined according to product characteristics, and the right containment solution has to be determined according to product and process properties (see below). With an ongoing trend of increasing API activity the potential risk for operators, even when using isolators, increases too.

Why would there be any risks using isolators since they help create safety for the operator and containment of environment for the API?

BEWARE OF THE HIDDEN RISKS ASSOCIATED WITH ISOLATORS

Pharmaceutical companies aren't paying enough attention to the hidden risks when using isolators from the manufacturing perspective, as well as the customer perspective. Most industry companies typically focus on specific key parameters of how the isolator should be created, answering the questions of the following properties:

Product Properties

- How hazardous is it?
- What is the operational exposure limit (OEL)?
- How much quantity should be handled? c?
- Is it in liquid or is it in powder form?
- Is it micronized powder, and therefore is it in the aerosol size?

Process properties

- Which kind of process/machine should be contained?
- How is the product arriving? In which quantities?
- How should the product be extracted from the isolator? In which quantities?

All these evaluations determine the way an isolator should be designed and manufactured, however there are other factors to consider. Hidden risks, which may be hazardous or even fatal for the operator, are not often analyzed when it comes to isolator use, manufacturing, and design.

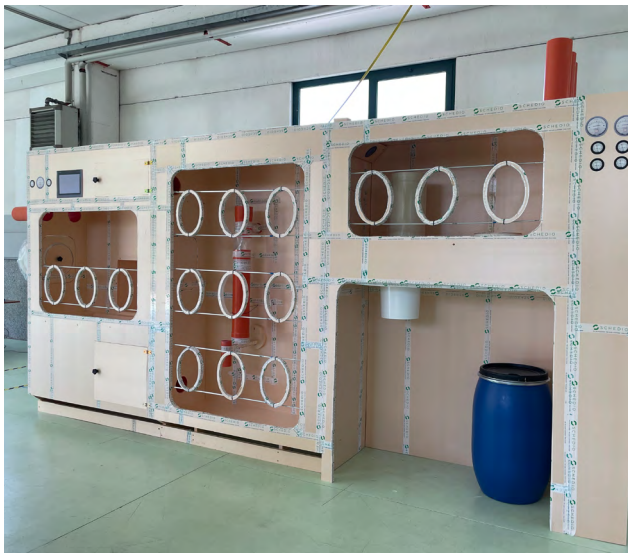
Some of these are related to the containment capabilities of the isolator, some other are related to the general safety of the machine, both equally dangerous.

Ergonomic Structure

Performance of a mock up study (a 1:1 scale reproduction of the machine) and simulation of the whole process focusing on transferring product and materials. Ergonomic problems can happen for operators, affecting not only the back and arms, but also if the operator bypasses safety barriers to save time and rush through the production process. Ergonomic Structure is often considered only with regards to comfort for the operator, but it is actually linked to the safety of the machine.

Gaskets Memory

Some isolators are manufactured with static gaskets to tighten the open points (e.g. between the frame and the window, or between two separate chambers attached together, like a pass box and the main chamber). With time passing by, these gaskets lose their flexibility, and with the use of aggressive solvents, there may be problems in guaranteeing the containment of the isolator as leaks may occur.



Gaskets Pressure Monitoring

In the case of using inflatable gaskets, since their performance is directly linked to their inflatability, it is really important to monitor their pressure throughout the use of the isolator, in order to make sure there are no leaks of product. Always consider that if a gasket is not perfectly tightened, the isolator may automatically run the fan faster in order to maintain the targeted negative pressure, with the operator not realizing that there is actually a leak. In addition, if there is a power failure, or a stop of the machine with the fan turned off, this may result in the product released outside the glove box.

Maintenance Accessibility

In order to ensure a proper maintenance, and make sure the isolator is able to always maintain the same containment level, it is important to allow an easy and accessible maintenance to all parts that may impact proper tightening of the isolator. As an example, gaskets located between two chambers, attached with a flange, must be easily accessible without the need to dismantle the isolator. This way it will be possible to perform more regular maintenance, and ensure that the gasket is always replaced and continuously performing as normal.

Operator Training

As the containment often depends strongly on operator skills, it is crucial to repeat the training on containment to operators from time to time, optimally on a yearly basis, in order to ensure that all the procedures for introduction and extraction of product, along with material being performed in the proper way. Mistakes in handling may result in a lower containment level, and an exposure to very toxic compounds, which may be fatal either in the short (e.g. tranquilizers, pain killers) or in the long term (causing tumors, etc.).

Centralized ventilation

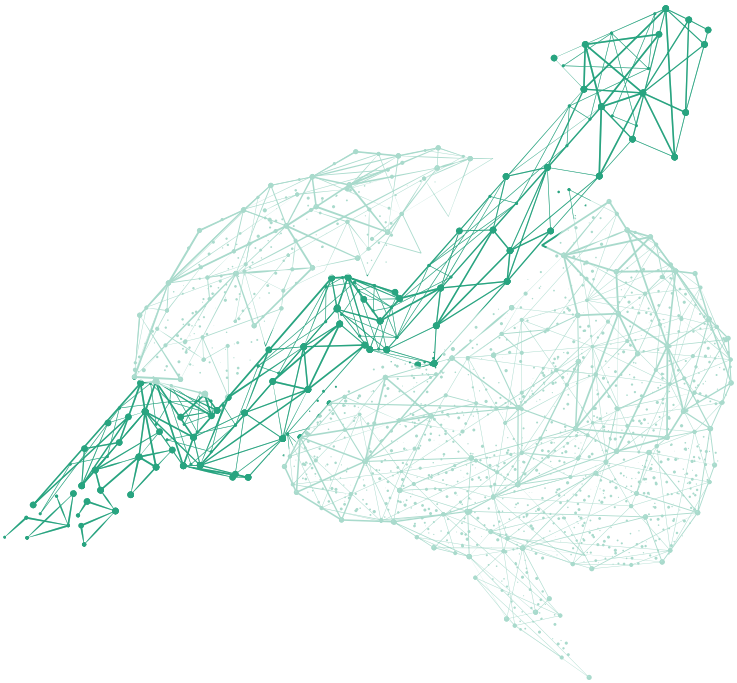
Sometimes customers use the ventilation system of the building, instead of using an owned, independent ventilation for the glove box. The systems seem to be centralized, with a valve that locally controls the negative pressure inside the isolator. However, isolators normally work on very fine pressure adjustments, and their own dedicated ventilation, but still connected to the centralized exhaust, is essential to ensure the containment level is respected and the operator's safety is guaranteed. Other machines in the building, or even the ventilation of the building itself may fail, resulting in compromising the safety of the machine, and therefore the safety of the operator.

Independent ventilation

Each glove box chamber shall have its own dedicated ventilation system, composed by HEPA filtration and dedicated fan. Without it, the chambers, which rely on other chambers for negative pressure, when isolated, may lose the negative pressure they have, resulting in a potential exposure to the internal particles for the operator. An independent ventilation also allows to have a chamber safe, even if other chambers are compromised (e.g. in case of a broken front glass).

Margin for Error

When designing a glove box, it is key to calculate some margin for error in the handling of the safety tools for introduction and extraction of product or material to it, and from the isolator, with regards to the overall containment level. Once the isolator is closed and with a regular leak test passed, the margin for mistakes is minimal. However, what really determines the containment level and containment performances of an isolator is the way the inlet/outlet is designed, as that's the part where the operator could be most exposed to the product. In most cases these operations are very manual (e.g. liners) and the containment performances strongly depend on operators' skills and performance. It is therefore crucial, especially with very high active compounds, to estimate this risk, and design the glove box to be intrinsically safe, leaving a certain margin for eventual minor mistakes done in the manual operations.



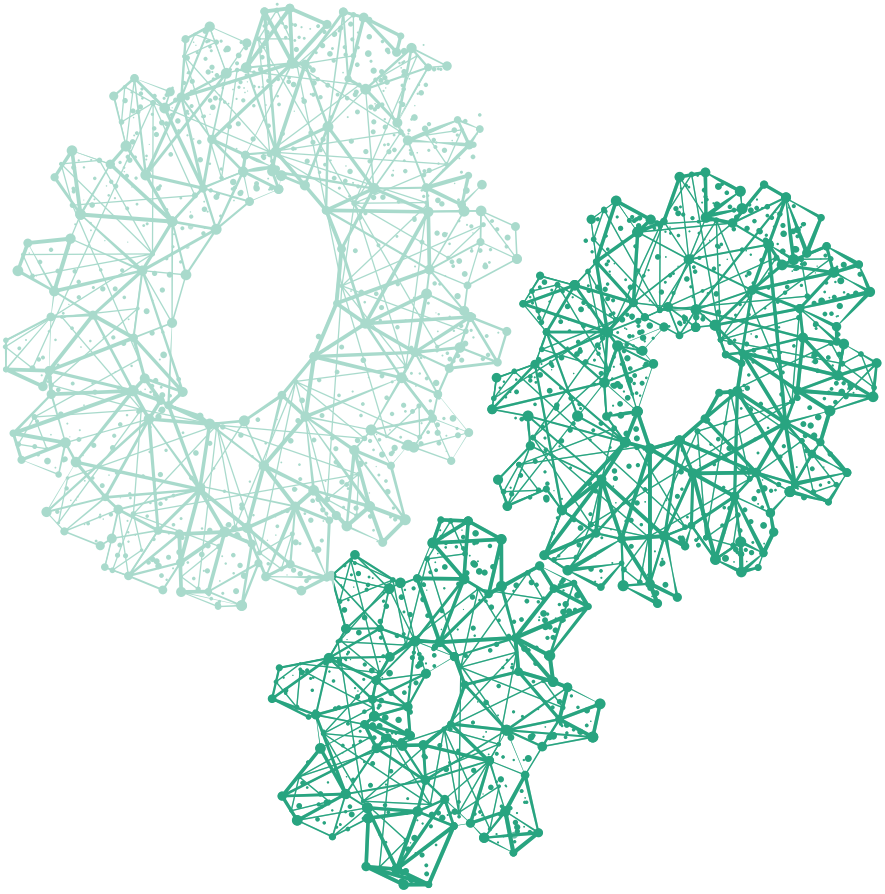
Other hidden strong risk factors, involving safety, but are not necessarily linked to a containment threat, should be considered… such as:

- Correct positioning of inlet and outlet of nitrogen, as in case of inert operations there could be bags of air: Sometimes the inside of the glove box must be inert, whether it's because the product to be handled is flammable, or because there's a washing procedure to be done with solvents. In these cases, the inside of the glove box must be flushed with nitrogen, so that by eliminating air, there won't be the comburent needed to cause an explosion. In each isolator's chamber there normally is one inlet of nitrogen, and one exhaust. It is crucial to position these two connections well, or else there is the strong risk to have "bubbles" of air, or zones not flushed with nitrogen inside the isolators. Even such zones could be enough, in the presence of a spark (either by a tool falling, or from electrostatic charges generated by the product or process) to cause an explosion, maybe close to the operator!

- Weight of objects: Front face isolators (not half suite ones) are the most utilized, and they imply that all the operations are handled with gloves through a window, with the operator standing and moving the parts while standing still. It is absolutely mandatory to reduce each individual part weight (whether the part is a component of the machine, or a bag of product) at least below 5 kg. This should be part of the mock up study performed BEFORE the manufacturing of the machine. If this parameter is not respected, there could be strong harm to the spine of the operator, and there could also be the risk of the operator not respecting safety procedures, to save its backbone from excessive weight. Not to mention the risk of parts falling on the hands of the operator, or damaging the machine.

- Independent drains: Each glove box chamber shall be treated independently from the others, not only from a ventilation point of view, but also from a washing drain point of view. The interconnections between different chambers shall be allowed and limited only to the opening of an internal connection (e.g. door, liner). As an example, washing with solvent, if the drain would not be independent (through a proper valve management), the isolator chamber that is being washed, would be in connection with another chamber already cleaned, perhaps with the front window open. The air from the open chamber would flow into the chamber being washed, because of the negative pressure inside it, creating the risk of explosion. And recent history has seen this happening unfortunately.

- Inertization while washing: It is absolutely mandatory that if you are washing with solvents, the operator is unable to open any window of the glove box, which may contain traces of solvent inside. A tool falling may indeed create a spark, resulting in the explosion of the machine.



THE SCHEDIO APPROACH TO *SAFETY BY DESIGN*

Schedio's safety by design helps pharmaceutical clients handle the meticulous procedures, developments, and changes during the entire process to help reach the final outcome.

"A machine must be designed for being intrinsically safe, not only when the operator follows the manual in full, but also when mistakes are made, or procedures are not properly followed. "

Our experience with isolator and operator safety is world-class. We are specialized on:

- Very high potent isolators with containment level of up to 1ng/m3 (0.001 microgram /m3)
- 360° safety, not only on the containment level of the machine, but on all the different aspects that may impact directly or indirectly on containment and safety, either in the short or long term.
- Operator training of best practices for containment… done yearly. (All operators must be certified to ensure the highest levels of safety and lower chances of risks while operating.)

We also help to enforce regular maintenance by the manufacturer of the isolator / glove box, with a long-run leak test, and performance of SMEPAC tests on a regular basis (at least once a year). This helps to verify the proper functioning of the machine and make sure best practices are in place with regards to hazardous product handling.
With Schedio, safety comes first. It's built in our culture and in every aspect of the design of all our machines. When operating machines, safety must be guaranteed not only from procedures in the technical manual, but also in case of eventual human error.

We have saved lives of operators by always valuing safety first.

This makes a difference in our *safety by design*.

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