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Isolators – Design and Application

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by Richard Denk

Looking at Annex 1, the use of barrier systems such as RABS or isolators is very common. Since Contamination Control Strategy (CCS) requirements are an important part of selecting the appropriate barrier technology, closed RABS or isolators should be preferred.

As isolators have the additional feature of automatic surface decontamination with vaporized or finely nebulized H_2O_2 compared to a closed RABS and can be installed in a grade C/D cleanroom area, isolator technology is more commonly used. It also offers the highest level of safety and is more sustainable, as it requires fewer cleanroom zones and associated airlocks with the energy-intensive room air technology they require.

Design and applications of isolators

Isolators are used in aseptic production in various areas. They are most frequently found in the handling of sterile products. These can be in liquid or also solid form (solids). Human or animal cells are also increasingly used in new therapeutics, e.g. for cell and gene therapies, which are also processed under aseptic conditions. Some examples of the use of isolators are presented below.

Isolators for the production of cell and gene therapeutics

Even though human or animal cells for use in new therapies cannot be considered sterile due to their collection method (mostly in hospitals), there is also a requirement here to protect the cells from further possible particulate or microbiological contamination. For this reason, isolators are increasingly used here as well. Since most isolators are closed isolators, installation in cleanroom grade D is possible.

Figure 1 Isolator for cell and gene therapy (courtesy of SKAN AG)

Isolators for filling sterile liquids

Most isolators for the aseptic handling of sterile products are found in area of filling sterile liquids. Large quantities are often filled there, especially in the production of vaccines. In addition to high-capacity filling systems, small-volume filling operations are also in use, often for filling special cell and gene therapeutics or other new highly active substances.

The design of specific filling lines is adapted to the containers for the sterile product to be processed (e.g. vials, syringes, etc.), or the lines are modularly convertable to the different formats.

Example: Setting up a filling line for vials

- Vial washing machine for the empty containers
- Hot air tunnel

As an alternative to the washer and hot air tunnel, pre-sterilized containers packed in tubs can also be used, which are fed into the isolator through an e-beam unit

- Filling of the sterile liquid in the isolator
- Insertion of the plugs in the isolator
- Optional step: freeze drying
- Flanging (sealing) in the isolator or also in a RABS with grade A air quality.

Since this example involves an open isolator (use of small openings (*mouse holes)* for insertion and/or removal of the vials), the filling system including isolator is installed in a grade C area.

Figure 2 Filling line with isolator for larger volume containers (courtesy of SKAN AG)

Isolators for sterility testing

As part of the quality assurance of sterile products, a sterility test is performed on the finished product batch at the end of the manufacturing process. The technology used (e.g. isolator) should provide the same aseptic conditions as those used in the manufacture of the medicinal product to avoid possible contamination. Sterility testing is an important component for the release of the finished product.

Figure 3 *Isolator for sterility testing (courtesy of SKAN AG)*

Isolators for aseptic manufacturing

The conditions inside an isolator for aseptic manufacturing should correspond to a grade A environment. To achieve this, some technical measures are required. Important aspects are the air quality (terminal HEPA-14 filter), the air velocity and a uniform laminar flow.

The design of the internals of the isolator along with the installed components also plays a significant role. An important aspect of the design is the consideration of the "First Air" (air coming out of the terminal HEPA-14 filter). This airflow should not be interrupted before it hits critical surfaces such as the open sterile containers.

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