Benefits of Barriers

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Barrier systems run the spectrum from simple process demarcation devices to full physical barriers, as is the case with isolators. With global expansion, the need to create well defined and controllable manufacturing environments, quickly and efficiently, has rekindled interest in isolator designs. Restricted access barriers (RABs) represent one of the fastest growing technology solutions for products that cannot be terminally sterilized.

Large cleanroom facilities have sophisticated air handling requirements and continuous energy demands. Facility design and operation are integral to the overall operability and sustainability; simplified cleanroom designs bring the benefit of reduced capital expense. Facilities must evaluate special design considerations relating to the use of barrier systems and their implications for compliance through methodology deployed in multiple pharmaceutical manufacturing markets around the world.

Isolators versus RABs

The objective of RABs and isolators is to isolate the process and the product from sources of potential contamination. In normal aseptic processing, the greatest potential source of contamination lies with the operators and the handling of sterilized components. Isolators typically have closed physical barriers, use closed transfer devices, and remain closed in operation following the last decontamination step and during processing.

In aseptic processing, bio-decontamination of the isolator barrier interior and associated process equipment non-product contacting surfaces are typically completed by a gaseous hydrogen vapor system. Gaseous decontamination of indirect product contact parts has also been applied in isolator technology.

Sterilized parts for aseptic processes inside an isolator barrier may use a clean-in-place (CIP) and sterilize-in-place (SIP) process or be sterilized-out-of-place and be aseptically transferred inside the barrier via an internally sterile closed transfer device, without compromise to sterility.

When operated as a closed system, sterilized parts and surfaces, together with products within the clean zone, are protected from bio-contamination from the surrounding environment and process operators. The U.S. Food and Drug Administration (FDA) Guidance for Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice, released in 2004, specifies that the interior of the isolator should meet Class 100 (ISO 5) standards. In the contamination risk reduction hierarchy, isolators, as closed systems, provide a higher level of risk reduction when compared to RABs.

Open versus closed RABs
The design and operation of a RAB’s configuration defines the level of contamination risk for an aseptic operation. The design of the RAB refers to the air handling design and the operation refers to the level of operator intervention allowed. Four basic configurations for RABs and their relative level of contamination control are shown in Table 1.

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<tr>
<th>RABs Configuration</th>
<th>Level of Contamination Control</th>
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<tr>
<td>Open Operation-Closed Design</td>
<td>Highest</td>
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<tr>
<td>Closed Operation-Open Design</td>
<td>Lowest</td>
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A closed operation RAB provides a higher level of contamination control because the RABs barrier doors remain closed from the point of the last bio-decontamination, through initial set-up through processing. These systems typically use transfer systems that are similar to isolator type transfer systems that are closed and dock with the RABs.

An open operation RAB, by definition, provides recognition that the barrier doors can be opened for operator intervention(s), at defined risk assessed stages during aseptic production operations, after the last bio-decontamination step. Open operation RABs are further characterized:

- **Type 1: Process Intervention** (highest contamination risk)
- **Type 2: Set-up Intervention** (high contamination risk)
- **Type 3: Inherent Closed Barrier Interventions** (lowest contamination risk)

Closed design RABs have a dedicated air handling system that provides down-flow air that circulates inside physical barriers, together with provision of fresh air make up and ducted exhaust systems. Materials transfer devices are either a fully closed system, e.g. alpha-beta rapid transfer ports, and/or devices that connect or interface under aerodynamic barrier protection and remain closed to the surrounding environment during the transfer procedures. Closed-design RABs may also include a gaseous decontamination system.

Open design RABs have an air handling system that is dedicated (termed “active”) or shared with the cleanroom ceiling down flow (termed “passive”) with air overspill to the surrounding environment. Overspill air is directed to a low level under the physical glove-barrier screens and below the points of critical operation, typically 300 mm below and away from the point of fill. Transfer devices may include closed or aerodynamic protection at the device-barrier connection location and maintain closed separation to the surrounding environment during the transfer procedure.

**Containment considerations**
By use of the established containment design features of physical barriers in combination with aerodynamic protection and pressure differentials, RABs may be specified for use in containment applications with a focus on operator protection. This is a key consideration when dealing with manufacturing operations that do not have as well-defined exposure control limits.

Decontamination

Most systems use a gaseous decontamination system combined with a physical cleaning and sterilization processing. Many isolators come equipped with clean-in-place/sanitize-in-place (CIP/SIP) systems to facilitate bio-decontamination. Demonstrating effective cleaning and bio-decontamination are required for both RABs and isolators, especially in the controlled ISO 5 processing area.

Implementation considerations

The challenge in implementing either RABs or isolator systems is the level of sophistication required to ensure aseptic processing conditions. When designing these systems the facility design and operation becomes an integral component of the overall operability. In Asia and Europe, the use of hydrogen peroxide vapor (HPV) to decontaminate not only the isolator but also the room outside the isolator has become common. To be effective, this means the rooms need to be sealable to preclude the HPV from leaking into adjacent areas. Similarly, the room returns need to be sealable to protect the HEPA filters from the HPV. These become critical to the HVAC design when employing passive design RABs that share the process air supply with room air supply systems. The process flow for sterilized components to the transfer station and then to the isolator or RABs requires more space than conventional aseptic processes, since the transfer stations are typically captive to the room.

Conclusion

Both isolators and RABs provide the benefit of reduced capital expense from simplified cleanroom designs. However, the cost savings realized from reduced cleanroom space
are often cannibalized by the cost of equipment and the on-going operating costs of supporting a RABs or isolator process. Both solutions require a clear understanding of the process contamination risk potential. Facility capabilities should be considered in tandem with process requirements, defined as all activities from decontamination through processing. The consideration of combining contamination control “features and functions” to set different performance levels, in terms of providing better sterility assurance and risk reduction, helps define both the groups of aseptic processing options and RABs. The defined options can then be set against user and regulatory requirements. By understanding the risks and benefits of isolator and RABs designs and their operation, an organization will be able to minimize the technical, compliance, and business risk of implementing these technologies.

References

2. Restricted Access Barriers - RABS definitions and performance, Bioquell, UK Ltd.

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