

ISPE Definition: Restricted Access Barrier Systems (RABS) for Aseptic Processing

by Jack Lysfjord

Introduction

Aseptic processing evolved in the 1980s and 1990s with the use of isolators to separate the operator from the "critical zone" and thus reduce product risk. Restricted Access Barrier Systems (RABS) are another way to reduce the interventions that can occur in cleanroom processing through the use of a barrier and dynamic air flow and can be a viable alternative to isolators.

Because people are the "dirtiest" part of aseptic processing, reducing interventions into the "critical zone" can impact very favorably the cleanliness in the finished product. RABS incorporates a "barrier" with HEPA filtered airflow to significantly reduce the "Probability of a Non Sterile Unit" (PNSU). Stewart Davenport of Upjohn (now Pfizer) in Kalamazoo, Michigan coined the RABS acronym in the early 1990s and presented data at the June 2001 ISPE Barrier Isolator Conference that showed media fill data from nine years of operation (almost a million cumulative media fills) from three filling lines with RABS yielded PNSU data similar to the use of isolators. Compared to isolators, RABS can allow for faster start-up time (agency approvals), ease of changeover, and reduced capital costs, particularly with retrofits and renovations.

RABS has an "S" that stands for system. Simply buying restricted access barrier hardware does not create a RABS. Many elements need to be in place to really have a RABS:

- properly designed equipment
- management oversight
- a quality system in place
- proper surrounding room design to maintain ISO 5 in critical zone
- proper gowning practice
- proper training

- initial high-level disinfection with sporicidal agent
- proper SOPs for rare interventions
 - disinfection
 - appropriate line clearance
 - documentation of event

The ISPE Barrier Isolator Technology Forums created the atmosphere for discussing the RABS definition issue. Discussions with user companies varied as to what constitutes a RABS. In discussions with Rick Friedman, FDA, many companies had been calling any enclosure a RABS whether or not it included the above-listed elements. Everyone was confused as to what is a RABS. He felt ISPE could help create a definition for RABS to help industry, the Agency and overall healthcare. We formed a committee comprised of RABS users, Agency representatives, and equipment manufacturers:

- Jack Lysfjord, *Valicare Division, Bosch Packaging Technology, USA*, Vice President, Consulting and Chairman of the RABS Definition Committee
- Michael Porter, *Merck and Company, USA*, Principal Engineer, Sterile Process Technology and Engineering
- John Shabushnig, PhD, *Pfizer Inc., USA*, Senior Manager, Global Quality Technical Services
- Joerg Zimmermann, *Vetter Pharma Fertigung GmbH & Co. KG, Germany*, Head of Aseptic Production
- Ian Symonds, *GlaxoSmithKline, UK*, Director Process Validation Global Quality
- Rick Friedman, *US Food and Drug Administration, Team Leader for Guidance and Policy, Division of Manufacturing*

and Product Quality in the Center for Drug Evaluation and Research (CDER)

We met via teleconference on almost a weekly basis for six months to come up with a concise definition for RABS. An interim definition was posted on the ISPE Web site for comment. All comments were put into a spreadsheet, ranked for importance, and evaluated. The end result is published below. We hope it is of benefit to help with evaluating the technology for future use.

We thank all who commented to the draft version. I, especially, want to thank the members of the committee for their energy, knowledge, and time.

ISPE Definition of RABS, 16 August 2005

Human operators pose the greatest risk to product contamination during "conventional cleanroom" aseptic processing. Many different barriers of varying capabilities have been used to separate operators from critical sites during aseptic processing with the objective of reducing the probability of a contaminated unit. These range from simple flexible curtains used on many traditional aseptic processing lines to advanced aseptic processing in isolators.¹ A Restricted Access Barrier System (RABS) is an advanced aseptic processing system that can be utilized in many applications in a fill-finish area. RABS provides an enclosed environment to reduce the risk of contamination to product, containers, closures, and product contact surfaces compared to the risks associated with conventional cleanroom operations. RABS can operate as "doors closed" for processing with very low risk of contamination similar to isolators, or permit rare "open door interventions" provided appropriate measures are taken.

Design

A RABS provides a level of separation between operator and product that affords product protection superior to traditional systems. There is no single design model for a RABS; however, these systems share the following common "quality by design" characteristics:

- Rigid wall enclosure² that provides full physical separation of the aseptic processing operations from operators.
- Unidirectional airflow systems providing an ISO 5 environment³ to the critical area.
- Sterilization-In-Place (SIP) is preferred for contact parts such as fluid pathways. Where this cannot be achieved, such parts should be sterilized in an autoclave, transferred to the RABS via a suitable procedure and aseptically assembled before processing.
- Product contact parts such as stopper feed and placement systems should be sterilized in an autoclave and aseptically assembled before processing.

- Entry of material such as environmental monitoring materials, consumables, containers and closures shall be via a suitable transfer system that prevents exposure of sterile surfaces to less clean classification environments.
- Use of glove port(s), halfsuit(s) and/or automation to access all areas of the enclosure which need to be reached by an operator during filling operations.
 - Gloves and gauntlets attached to glove ports are required to be sterile when installed; thereafter, gloves should be sanitized or changed as appropriate to minimize the risk of contamination.⁴
- "High-level disinfection"⁵ of all non product contact surfaces within the RABS with an appropriate sporicidal agent before batch manufacture.⁶
- Surrounding room classification should be ISO 7 minimum in operation.³
- Some processes may include rare open door interventions. In these cases, because of the inherently increased risk to product, the following are required to maintain the RABS protection concept:
 - Provision for disinfection of non-product contact surfaces using appropriate decontaminating agents following a door open intervention.
 - Locked door access or interlocked door access with recorded intervention alarms (and/or other satisfactory means of documentation) and mandated appropriate line clearance.
 - Positive airflow from the enclosure to the exterior environment while the door is opened.
 - Appropriate ISO 5 classification³ areas may be necessary immediately adjacent to outside of enclosure to always assure ISO 5 conditions³ inside the RABS. Examples of such situations are:
 - § Setup of oversized sterile equipment that requires unwrapping of autoclave packaging outside of the RABS.
 - § Any machine sections that require open door interventions (such as certain powder filling applications). After any open door intervention, operations cannot re-start until ISO 5 conditions³ are re-established in the critical zone.

Operation

When aseptic filling operations are carried out in a RABS, it is the intent to eliminate the need to open RABS doors

after thorough sporicidal disinfection of non product contact surfaces. Design to prevent door openings can be achieved by a number of measures which include Clean-In-Place/Sterilize-In-Place (CIP/SIP) to the point of fill for liquid filling operations, remote or automated sampling for In-Process Control (IPC) testing including monitoring for viable and non-viable particles, and the use of enclosed transfer systems which offer greater protection during introduction of components and pre-sterilized equipment. Another key measure includes automation, use of glove ports, and/or use of half suits to eliminate need for “open door” interventions.

When open door interventions are necessary⁷, an ISO 5 (class 100)³ vertical unidirectional airflow system outside of the RABS reduces risk of a breach in ISO 5 conditions³ and further safeguards the aseptic integrity of the system. Each intervention that requires opening of a door of the RABS is regarded and documented as a significant event. Interlocked RABS doors facilitate control and documentation. Following an open door intervention, appropriate line clearance and disinfection commensurate with the nature of the intervention are required as outlined in the standard operating procedures.

Footnotes

1. A decontaminated unit, supplied with ISO 5 (100 part/ft³ at (0.5 microns) or higher air quality, which provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding cleanroom air and personnel). *Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*, September 2004.

ISO 14644 Cleanrooms and associated controlled environments – Part 7: Separative Devices (clean air hoods, gloveboxes, isolators, and mini environments), 2004.

EUDRALEX Volume 4 – Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice – Annex 1, May 2003.

2. There are occasions where containment of toxic materials is required and special closed or containment RABS may be used.
3. All room classifications are “in operation” and include appropriate microbial action levels in Table 1 of Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004.
4. Section V, Personnel Training, Qualification, and Monitoring, *Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*, September 2004.
5. High-level disinfectants are defined as “capable of destroying all organisms with the exception of high numbers of resistant spores,” adapted from Block, S., *Disinfection, Sterilization, and Preservation*, Fourth Edition, 1991, and the *Manual of Clinical Microbiology*, Sixth Edition, p.232.
6. In certain circumstances, multiple day operations are possible depending on design, appropriate disinfection plan, risk mitigation steps, early regulatory review (i.e., pre-operational review is recommended), and a subsequent ongoing evaluation of process control data.
7. Product contact parts need to be sterilized and their sterility must be maintained. When appropriate, fitting of oversize equipment (such as stopper feeding parts) during filling setup should be followed by appropriate and thorough disinfection (product contact parts need to be sterilized). 