

Containment Planning for the Next Generation of Advanced Therapies

By Farid Adel

Emerging advanced therapies, are changing the assumptions behind containment and pharmaceutical facility design.



Highly potent active pharmaceutical ingredients (HPAPIs) are changing the assumptions behind pharmaceutical facility design. Compounds used in oncology, immunotherapy and other targeted therapies can deliver significant therapeutic value at low doses, but that potency also increases the consequences of worker exposure, cross contamination and process deviation.

For manufacturers, containment is no longer a specialized feature added around a process. It is a central design requirement that affects architecture, process flow, automation, utilities, validation, cleaning, sustainability and long-term operational flexibility.

Why Containment Strategy Matters

Advanced therapies are moving from development into commercial production, increasing demand for facilities that protect personnel while maintaining product integrity and meeting regulatory expectations. That balance can be difficult in multiproduct sites, legacy buildings or clinical manufacturing environments where product changeovers are frequent and process definitions may still be evolving.

A contamination control strategy (CCS), or equivalent risk-based containment strategy, brings together process understanding, occupational exposure limits (OELs), facility zoning, equipment selection, cleaning validation and operating procedures. It should account for the full path of material through the facility, from raw material receipt through dispensing, formulation, filling, packaging and waste handling. The strategy also should be tested against routine and nonroutine conditions, including maintenance, glove failure, transfer interruptions, equipment cleaning and batch changeover.

Containment breaches rarely occur only at obvious points. A manufacturing suite may include isolators, pressure cascades and high-efficiency particulate air (HEPA) filtration, yet still face exposure risk during sampling, drum docking, waste removal or movement between zones. A strong strategy looks at those interfaces as carefully as it reviews the primary process equipment.



Figure 1: Containment Road map. Steps for managing containment in the pharmaceutical manufacturing process for facilities handling toxic products.

Common Containment Pain Points

- **Worker safety:** HPAPIs may require advanced containment systems to reduce exposure while supporting operator ergonomics.
- **Contamination management:** Even minor contamination can affect product integrity, batch disposition and regulatory compliance.
- **Bioburden control:** Aseptic manufacturing environments utilizing technologies such as biosafety cabinets, closed restricted access barrier systems (cRABS) and isolators and associated bioprocess equipment require tight microorganism control to support reproducible operations.
- **Regulatory compliance:** Containment practices must align with regulatory expectations and be supported by objective evidence.
- **Process efficiency:** Complex containment systems can create bottlenecks if workflow, cleaning and transfer steps are not designed together.

The containment process works most effectively when teams evaluate these pain points across the full manufacturing sequence, from material receipt to waste handling. Figure 1 shows the steps for managing containment in pharmaceutical manufacturing facilities handling toxic products.

Facility Design, Zoning and Pressure Control

For HPAPI production, facility zoning and pressure control remain fundamental. Many HPAPI facilities use negative pressure regimes at room level, although sterile operations may combine negative-pressure rooms with positive-pressure product protection zones inside isolators. This helps limit particle migration during personnel or material movement. Directional airflow, air change rates, pressure alarms and environmental monitoring must be

coordinated with process needs so the facility supports containment without creating unnecessary utility demand.

Following a risk assessment, an effective CCS should address:

- **Cleaning and decontamination:** Surfaces should support residue removal. Materials such as 316L stainless steel and epoxy coatings resist chemicals and reduce residue retention.
- **HVAC and air handling:** HEPA filtration, pressure differentials and controlled airflow help prevent airborne exposure. Real-time monitoring supports containment performance.
- **Operator protection:** Engineered controls are preferred because they reduce direct operator exposure. Personal protective equipment should remain the last line of defense.
- **Primary and secondary containment:** Isolators, cRABS and controlled environments provide multiple layers of protection for operators and products.
- **Zoning and segregation:** Risk-based zones separate high-exposure areas from lower-risk operations, reducing cross-contamination potential.

Choosing Containment Technology

Equipment selection is a major decision point. Isolators and cRABS can both support aseptic operations, but they are not interchangeable. While both technologies can support aseptic processing, isolators generally provide substantially higher level of operator and product separation and are therefore more commonly selected when containment of highly potent compounds is required.

Isolators provide a sealed environment that separates operators from the process through glove ports and controlled decontamination. They typically provide stronger containment for potent and highly potent compounds, especially where OELs are very low. Figure 2 compares the containment technology options by

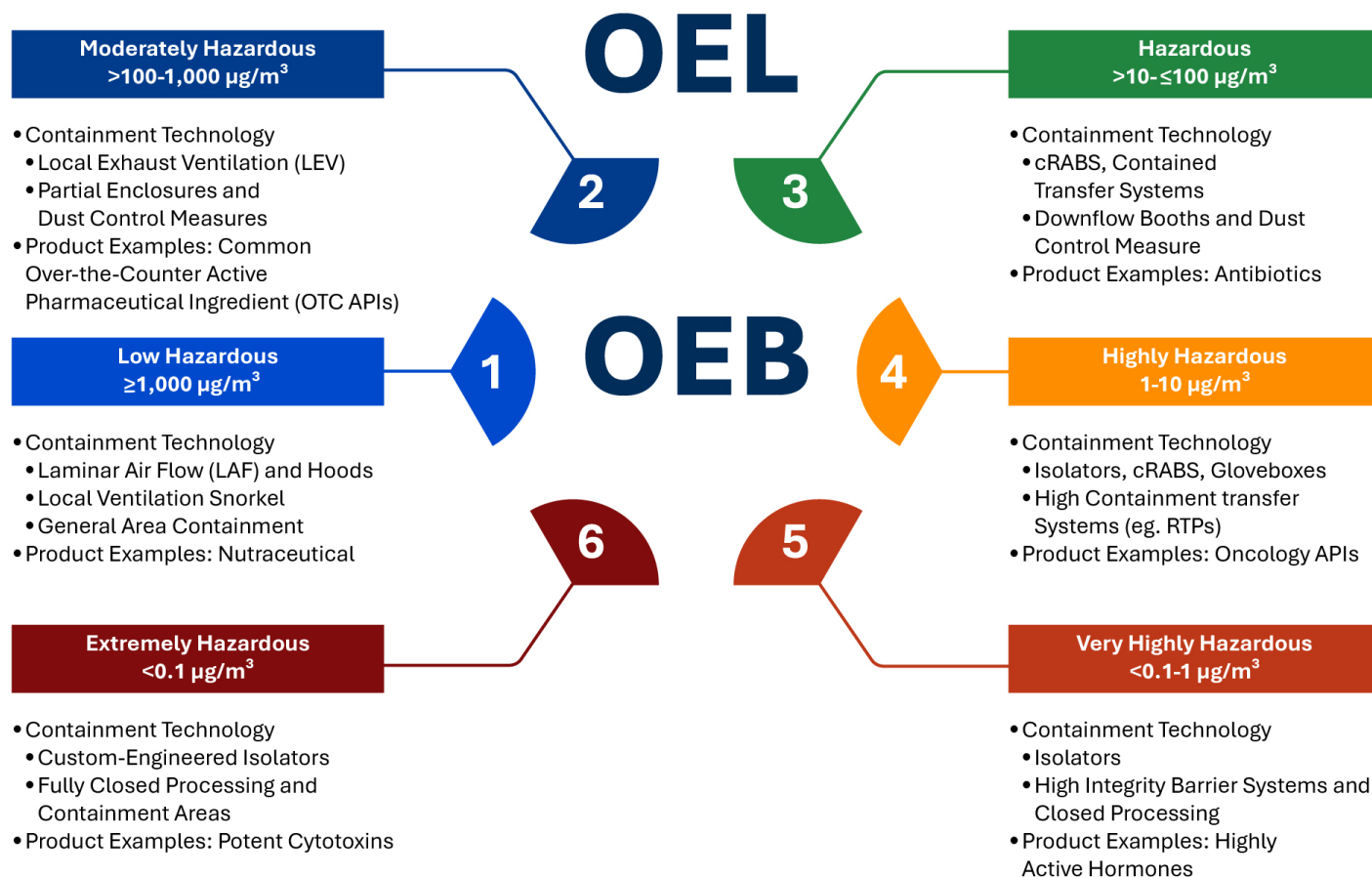


Figure 2: Suitable Containment Technology by Exposure Level. This matrix compares levels of containment from open handling to glovebox isolators, OEL ranges, and typical use cases.

OEL range and typical use case. cRABS can be effective in the right application, particularly when retrofit conditions, floor space or capital constraints limit the feasibility of isolators.

The final decision should come from a formal risk assessment that considers product toxicity, material properties, process steps, cleaning requirements and facility limitations.

Material Transfer: A Critical Interface

Material transfer often becomes the hardest part of the containment equation. Powders, liquids, tools, waste and packaging components must move without exposing operators or compromising cleanroom classifications.

Closed material transfer systems, including split butterfly valves, alpha-beta ports, rapid transfer ports, disposable transfer bags with integrated liners and decontamination chambers using vapor-phase hydrogen peroxide, can reduce open handling during high-risk steps. In larger facilities, robotic trolleys, automated guided vehicles or autonomous mobile robots can move sealed containers through airlocks while tracking material flow through digital systems.

These systems require close coordination among process, mechanical, architectural and automation teams so containment equipment works with logistics rather than becoming a bottleneck. Figure 3 shows how a risk assessment workflow connects containment decision points, responsible parties and required inputs.

Automation, Robotics and Digital Tools

Automation can reduce direct operator interaction with hazardous compounds. Automated dispensing, weighing, sampling and filling systems can shift repetitive or high-risk tasks away from manual operation. Robotic arms inside isolators or gloveboxes can handle vials, tubes and containers with consistent motion, improving batch-to-batch repeatability while limiting exposure. Automated systems can also reduce variability associated with manual interventions, which are often a significant source of both contamination and exposure events.

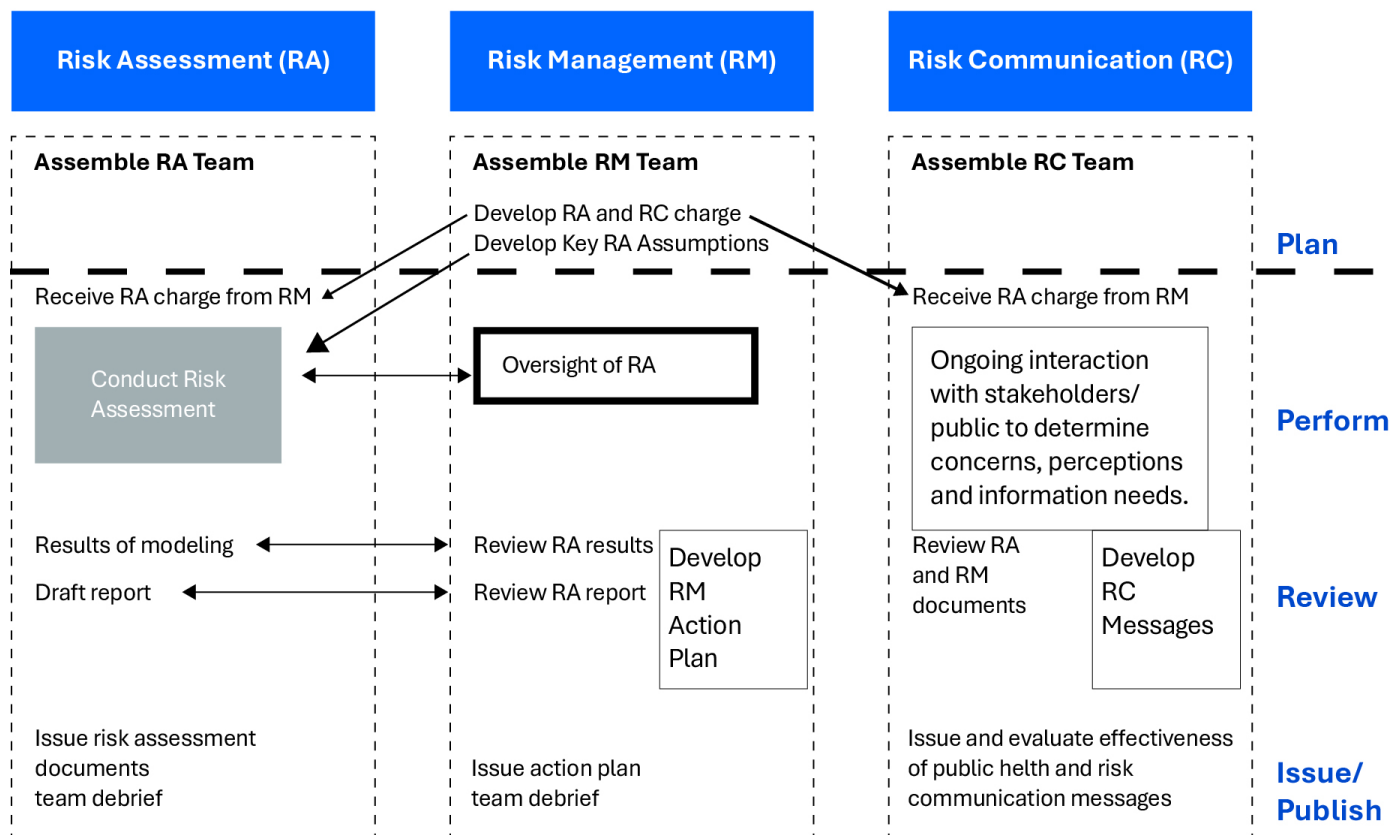


Figure 3: Risk Analysis Activities and Responsible Parties. A successful CCS relies on a thorough risk assessment process that includes specific tasks and information about who is responsible for each activity. Source: FDA.

Automation also strengthens documentation. Smart systems can log activities and process parameters, giving teams real-time data for audits, deviation investigations and continuous improvement.

Digital tools are strengthening containment planning before facilities are built. Computational fluid dynamics can simulate airflow and particle movement around equipment openings, door swings or failure scenarios. Digital twins can monitor pressure, temperature and air velocity over time, helping teams identify deviations and maintenance needs. Virtual reality can support operator training by allowing staff to practice gowning, transfer protocols and cleaning procedures before entering active highly potent manufacturing areas.

These tools do not replace engineering judgment, but they can help teams test assumptions earlier and reduce late design changes.

Cleaning Validation and Sustainability

Cleaning validation is central to containment performance. Equipment geometry, surface finish and material compatibility directly influence residue removal. Dead legs, exposed threads and irregular welds can trap potent residue and make cleaning harder to validate.

Engineers should evaluate riboflavin coverage studies where applicable, swab recovery trials, worst-case residue studies, automated clean-in-place and decontamination-in-place systems, electropolished stainless steel, polyvinylidene fluoride coatings and compatible valve linings. These decisions affect both operator exposure and the repeatability of cleaning validation.

Sustainability adds another layer to containment design. High-containment facilities can consume significant energy, water and cleaning chemicals. Isolators, heating, ventilation and air conditioning systems, HEPA filtration and decontamination systems must operate reliably, often under strict pressure and monitoring requirements.

Facility planning should evaluate recirculated air loops, heat recovery, variable frequency drives, demand-controlled ventilation and other utility strategies that reduce consumption without weakening containment. Single-use technologies can reduce water-intensive cleaning cycles but may increase solid waste, so life cycle environmental impacts should be evaluated rather than focusing solely on water or energy consumption. Figure 4 compares separation methods, including the relative reliability of physical barriers and aerodynamic separation.

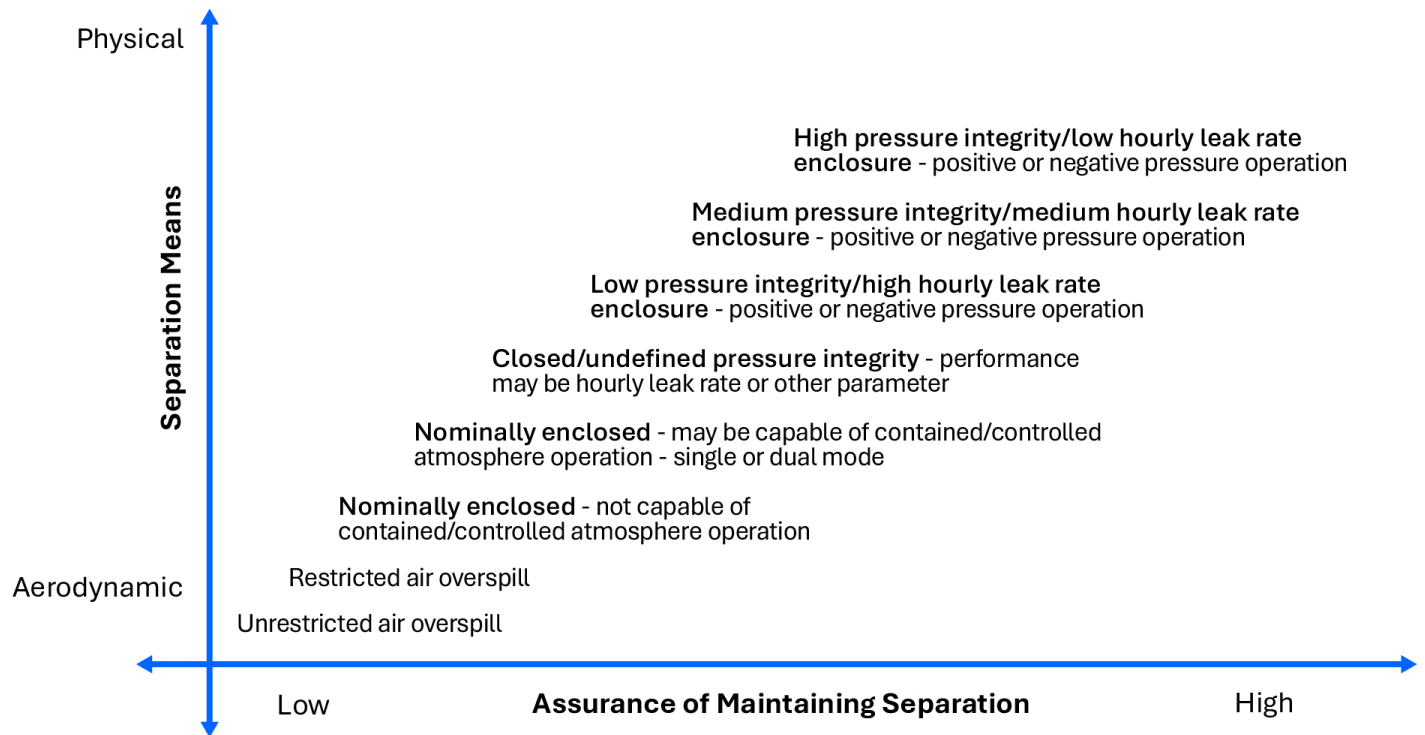


Figure 4: This figure illustrates how different separation methods correlate with their ability to reliably maintain separation, with physical barriers generally offering higher assurance than aerodynamic ones. (Source: Reproduced from ISO 14644-7:2004, American National Standards Institute on behalf of the International Organization for Standardization).

Planning for Flexible, Future-Ready Facilities

For legacy sites, modular approaches can help manufacturers add contained production capability without disrupting adjacent operations. Prefabricated cleanroom modules can be configured with dedicated HVAC systems, pressure cascades and isolator interfaces. This can support early-phase clinical production, multiproduct manufacturing and faster technology transfer.

The next phase of highly potent manufacturing will require containment systems that are tighter, more flexible and easier to verify. Continuous manufacturing, smart isolators, real-time sensor networks and automated material handling can reduce open transfers and support better process control.

At the same time, technology cannot substitute for front-end planning. The strongest containment strategies begin with a clear understanding of the product, the process and the people who will operate the facility.

As advanced therapies become more targeted and potent, containment will influence speed to market, facility utilization, sustainability and worker safety. Thoughtful design helps manufacturers protect personnel, preserve product quality and adapt to changing production needs without rebuilding core infrastructure.

Successful containment programs integrate facility design, equipment selection, operational controls and life cycle risk management into a single strategy that evolves with the product and process.

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