Isolators v. RABS: Facility Design Considerations for a Fill-Finish Suite

John R. Chester
Principal Engineer
Global Pharmaceutical Supply Group (J&J)
Raritan, NJ USA
908-927-3966

Credit – Developed in concert with Les Edwards (CEO Isogen) for ISPE
Outline

- Isolator Systems and RABS
  - Key notes from the Sept 2005 FDA Guidance
  - RABS Definitions
  - ISPE / FDA Position Paper
  - Key Benefits and Limitations

- Facility Approach Analysis
  - Capital “Savings” with RABS
  - Facility Cost Comparison (Iso vs. RABS) on Vial Fill/Lyo Line
  - Facility Layout Issues – Syringe RABS Line
  - Total Facility Cost Comparison – Iso vs. RABS

- Conclusions
Key Advantages of Isolators noted in the FDA Guidance Doc

- Minimize the extent of personnel involvement
- Separates the external cleanroom environment from the aseptic processing line.
- Emphasizes that the isolator must be…
  - Well designed
  - Supported by adequate procedures
  - Properly monitored
  - Properly controlled
- Provides warning that should not adopt a false sense of security
- Also acknowledges need to establish new procedures addressing issues unique to isolator systems.

- All of the above also apply to RABS
Summary of FDA Guidance on Isolators

- Appendix acknowledges the advantages of isolation technology, but warns that vigilance with good aseptic technique and procedures is still critical.
- Human interventions represent significant risks, especially glove interventions. This is mentioned repeatedly.
- Use glove integrity testing, microbial monitoring, under-gloves, sanitization, and sterile tools to minimize risk of personnel contaminating the enclosed aseptic process.
- If a material can be steam sterilized, then it should be.
- Background classification of 100,000 (ISO 8) and interior Class 100 (ISO 5). *Does not apply to RABS
Restricted Access Barrier Systems (RABS)

- **Barrier is a generic term…**
  - Flexible curtains
  - Rigid polycarbonate or glass enclosures (limited access barriers - LABS)
  - Rigid enclosure w/ gloves, RTPs, half-suits, automation (restricted access barrier system – RABS)

- **Basic Design Principles**
  - Unidirectional HVAC system to provide Class 100 / ISO 5 / Grade A environment.
  - Transfer systems (such as RTPs, UV, eBeam, etc…)
  - High-level disinfection of all interior surfaces (sporicidal) before batch manufacture (or after open door intervention)
  - Surrounding room ISO 7 (Grade B) minimum
Restricted Access Barrier Systems (RABS)

- More ‘Controversial’ Design Principles (from the ISPE/FDA RABS Position Paper)
  - If you decide to open the door (still considered RABS, but actually LABS in my book)
    - Door opening considered a significant event!
    - Disinfection after intervention (therefore, full line clearance)
    - Interlocked door access with recorded intervention alarms and line clearance.
    - Positive pressure (positive airflow) from inside to outside the barrier – this is tougher than it sounds
    - Additional ISO 5 space SURROUNDING the RABS for open door intervention protection (under the door swing)
The driving reasons for RABS

- Primary – reduction in capital equipment costs
  - RABS are typically less complex and cheaper than isolators
  - Typically no automated disinfection system (H₂O₂ or others)
  - But, significant impact of facility HVAC costs must be included in the evaluation.
    - Surrounding room must be Grade B/ISO 7 (instead of C or D) – some area possibly must be Grade A/ISO 5 for ‘door swing’
    - Increased costs of gowning, including gowning materials and productivity losses
    - Additional airlocks increases square footage of suite
    - Increased environmental monitoring for surrounding ‘A’ and ‘B’ areas
The driving reasons for RABS

- Secondary – perceived reduction in validation costs and schedule
  - But, no automated disinfection system (H2O2 or others)
    - Must still provide data on a non-automated high-level disinfection method of all interior surfaces (sporicidal)
    - Must still provide residue effects and disinfectant removal data
  - But, increased environmental qualification and monitoring costs for Grade A/B versus C/D area.
  - But, same costs for transfer systems validation versus an isolator (such as RTPs, UV, eBeam, etc…)
Case Study #1: Iso vs. RABS
Integrated Vial Fill/Lyo Line

- Integrated Filling/Lyo>Loading
  - 250 vial/min filler (2-20mL)
  - 3x25m² lyophilizers
  - TCAR-based lyo loading system

- Initial Design: Fully Isolated System

- Re-design: Utilize RABS for perceived increased flexibility for modified product mix

- Results…
  - Layouts (subsection of facility)
  - Capital Cost Comparison
  - Operating Cost Comparison
Initial Layout with Isolators

<table>
<thead>
<tr>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sq. Ft.</td>
<td>270</td>
<td>0</td>
<td>2820</td>
</tr>
</tbody>
</table>
Redesigned w/ RABS

<table>
<thead>
<tr>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sq. Ft.</td>
<td>418</td>
<td>2972</td>
<td>340</td>
</tr>
</tbody>
</table>
Current Layout

<table>
<thead>
<tr>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sq. Ft.</td>
<td>906</td>
<td>2583</td>
<td>340</td>
</tr>
</tbody>
</table>

Note: Room Classification Legend based on I.A.U.'s "Guideline for Design and Construction of Production Facilities, Manufacturing Operation and Cleanrooms", Section 7.1 Attachments and Forms- 7.1 Table 1, "Class Guide Designation and Equivalency with other Requirements"
## Cost Analysis – Initial Capital Case #1

<table>
<thead>
<tr>
<th></th>
<th>Est. Cost per Sq. Ft.</th>
<th>Iso Area</th>
<th>Iso Cost</th>
<th>RABS Area</th>
<th>RABS Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital Costs - Equipment</td>
<td></td>
<td></td>
<td>$ 4,750,000</td>
<td></td>
<td>$ 2,850,000</td>
</tr>
<tr>
<td>A/ISO 5 Area</td>
<td>$ 900</td>
<td>270</td>
<td>$ 243,000</td>
<td>906</td>
<td>$ 815,400</td>
</tr>
<tr>
<td>B/ISO 7 Area</td>
<td>$ 700</td>
<td>0</td>
<td>-</td>
<td>2583</td>
<td>$ 1,808,100</td>
</tr>
<tr>
<td>C/ISO 8 Area</td>
<td>$ 500</td>
<td>2820</td>
<td>$ 1,410,000</td>
<td>340</td>
<td>$ 170,000</td>
</tr>
<tr>
<td>Airlock / Gowning Area</td>
<td>$ 600</td>
<td>400</td>
<td>$ 240,000</td>
<td>1000</td>
<td>$ 600,000</td>
</tr>
<tr>
<td><strong>Total Estimate</strong></td>
<td></td>
<td>3490</td>
<td><strong>$ 6,643,000</strong></td>
<td>4829</td>
<td><strong>$ 6,243,500</strong></td>
</tr>
<tr>
<td><strong>Net Savings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>$ 399,500</strong></td>
</tr>
</tbody>
</table>
Cost Analysis – Initial Capital
Case #1

- Isolator Facility –
  - Capital Equipment Cost
    - Initial cost savings expected to be > $2 Million
    - Base cost savings appears to be < $500K
    - Additional costs…
      - Grade A space expansion and air return handling ($>100K + design fees)
      - Uncertainty in RABS regulatory response (chose conservative approach)
  - Net Result:
    - Re-design from iso to RABS saved little capital cost.
    - Additional ‘flexibility’ driver was reduced w/ increased production steps and floor plan changes.
Case Study #2: RABS Syringe Filling Line

- Restricted Access Barrier Syringe Fill Line
  - 300 Syringe/min filler (B-D Hypak Tubs)
  - Manual tub disinfection upon entry
  - ‘Conventional’ facility layout

- Results...
  - Tub Entry and Handling Layouts
  - Component Prep / Handling Areas
  - Filling Room Layout
Tub Handling and Entry Layouts

Tub Transfer Flow
Unclassified (1194)
- Grade D
- Grade C
- Grade B
- Grade A
- Grade B
- Grade C
- Grade D
- Unclassified (1185)

RABS Layout

<table>
<thead>
<tr>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ft²</td>
<td>20</td>
<td>100</td>
<td>870</td>
</tr>
</tbody>
</table>

Isolator Layout

<table>
<thead>
<tr>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ft²</td>
<td>20</td>
<td>0</td>
<td>970</td>
</tr>
</tbody>
</table>
Syringe Line: Filling Room Layout

<table>
<thead>
<tr>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ft²</td>
<td>330</td>
<td>510</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ft²</td>
<td>110</td>
<td>0</td>
<td>730</td>
</tr>
</tbody>
</table>
Syringe Line:
Other Area Layouts

Component Prep
Washing
Pass-through Autoclaves and Sterile Staging
Change Parts Clean Storage
Airlocks
Grade B Corridor

<table>
<thead>
<tr>
<th>RABS Layout</th>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ft²</td>
<td>150</td>
<td>800</td>
<td>1500</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isolator Layout</th>
<th>Area</th>
<th>A</th>
<th>B</th>
<th>C+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ft²</td>
<td>150</td>
<td>N/A</td>
<td>2300</td>
<td></td>
</tr>
</tbody>
</table>
## Cost Analysis – Initial Capital Case #2

<table>
<thead>
<tr>
<th>Area</th>
<th>Est. Cost per Sq. Ft.</th>
<th>Iso Area</th>
<th>Iso Cost</th>
<th>RABS Area</th>
<th>RABS Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital Costs - Equipment</td>
<td></td>
<td></td>
<td>$ 1,500,000</td>
<td></td>
<td>$ 750,000</td>
</tr>
<tr>
<td>A/ISO 5 Area</td>
<td>$ 900</td>
<td>170</td>
<td>$ 153,000</td>
<td>500</td>
<td>$ 450,000</td>
</tr>
<tr>
<td>B/ISO 7 Area</td>
<td>$ 700</td>
<td>0</td>
<td>$</td>
<td>-</td>
<td>$ 1,022,000</td>
</tr>
<tr>
<td>C/ISO 8 Area</td>
<td>$ 500</td>
<td>4000</td>
<td>$ 2,000,000</td>
<td>2320</td>
<td>$ 1,160,000</td>
</tr>
<tr>
<td>Total Estimate</td>
<td>4170</td>
<td></td>
<td>$ 3,653,000</td>
<td>4280</td>
<td>$ 3,382,000</td>
</tr>
<tr>
<td>Net Savings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$ 271,000</td>
</tr>
</tbody>
</table>
Cost Analysis – Initial Capital
Case #2

- Isolator Facility –
  - Capital Equipment Cost
    - Initial cost savings expected to be > $1.5 Million
    - Base cost savings appears to be approx. $250K
    - Additional costs…
      - Grade A space expansion and air return handling ($>100K + design fees)
  - Net Result:
    - Design from iso to RABS saved little capital cost.
Additional Cost Analysis – Applies to either Case #1 or #2

- **Validation**
  - Equipment IQ/OQ
  - Equipment PQ
  - Facility Qualification

- **Operating Expenses**
  - Gowning
  - Productivity
  - Changeover Process
  - Utilities
  - Maintenance
  - Revalidation

- **Environmental Monitoring**
  - Facility
  - Equipment / Isolators
Cost Analysis - Validation

- **Equipment Qualification** – (RABS Cost Savings - $50-$75 K)
  - Isolator and Gassing System IQ/OQ: 4-6 weeks
  - RABS IQ/OQ: 2-4 weeks

- **Performance Qualification** – (RABS Cost Savings - $80-$150K)
  - Isolator Gassing PQ - 12 weeks
  - RABS Manual Disinfection Process PQs – 8 weeks

- **Facility Qualification** – (RABS Cost Increase $75-100K)
  - Increased Grade A Space
    - More HEPA certifications
    - More viable air, particulate, and surface monitoring

- **Net Validation Savings w/ RABS = approx $100K and 2-4 weeks (critical path)**
Cost Analysis – Operating Expenses

- **Gowning**
  - Higher level gowning in RABS ‘B’ space (5 people, 4 changes per day, 5 days per week, 40 weeks per year x $75 per gown = $300K/year) – conservative (single shift - does not include supervisory, cleaning crews, monitoring personnel, other support)
  - **Summary:** RABS costs >$300K more per year

- **Productivity**
  - Higher level gowning w/ RABS – time to enter/leave
  - More airlocks w/ RABS
  - Increased cleaning and monitoring w/ RABS, including manual decontamination vs. automated H2O2 gassing.
  - Personnel comfort, motivation improved w/ isolators
  - **Summary :** RABS reduced productivity
Cost Analysis – Operating Expenses

- **Changeover Process**
  - Perception that flexibility comes w/ RABS, but very similar steps required, some more restrictive.
  - Set-up and cleaning of isolator can be done fully open, then close and gas automatically (less manpower intensive).
  - Glove testing/set-up similar w/ RABS and isolator
  - Set-up and cleaning of RABS can be done fully open, then manual disinfection process must begin w/ doors open is specific order, ending w/ glove disinfection w/ closed doors. Difficult handling for aseptic placement of stopper bowl and other autoclaved components.

  - **Summary:** RABS increased changeover process time
Cost Analysis – Operating Expenses

- **Utilities**
  - RABS requires more power to run larger HVAC units

- **Maintenance**
  - PMs on Equip vs. HVAC may be similar
  - Increased HEPA certifications (more in RABS facility)
  - Glove Testing and Replacement (similar on both)

- **Annual Revalidation**
  - H2O2 Gassing typical 3-5 days (cost $20-30K)
  - Manual process potentially less revalidation testing.
## Cost Analysis – Operating Expenses (Environmental Monitoring)

<table>
<thead>
<tr>
<th>Area</th>
<th>Sample Freq</th>
<th>Iso Samples</th>
<th>Iso Annual Cost</th>
<th>RABS Samples</th>
<th>RABS Annual Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A Area</td>
<td>continuous/per run</td>
<td>12 air, 40 surface</td>
<td>$1,040,000</td>
<td>18 air, 60 surface</td>
<td>$1,560,000</td>
</tr>
<tr>
<td>Grade B Area</td>
<td>per run/daily</td>
<td>0</td>
<td>$</td>
<td>8 air, 40 surface</td>
<td>$960,000</td>
</tr>
<tr>
<td>Grade C Area</td>
<td>weekly</td>
<td>12 air, 80 surface</td>
<td>$368,000</td>
<td>7 air, 40 surface</td>
<td>$188,000</td>
</tr>
<tr>
<td><strong>Total Estimate</strong></td>
<td></td>
<td></td>
<td>$1,408,000</td>
<td></td>
<td>$2,708,000</td>
</tr>
<tr>
<td><strong>Net Cost w/ RABS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>($1,300,000)</strong></td>
</tr>
</tbody>
</table>

*Cost Basis = $100/sample. Operation 5 days/week @ 40 weeks/year

**Represents an cost INCREASE w/ RABS, not savings.*
## Cost Analysis – Summary

<table>
<thead>
<tr>
<th>Item</th>
<th>Iso</th>
<th>RABS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Capital – Barrier Equipment</td>
<td></td>
<td>✓</td>
<td>RABS Saves $1.5-$2 Million</td>
</tr>
<tr>
<td>Initial Capital - Facility</td>
<td>✓</td>
<td></td>
<td>RABS Costs &gt;$1.2-1.5 Million</td>
</tr>
<tr>
<td>Validation</td>
<td></td>
<td>✓</td>
<td>RABS Saves $100K and 2-4 weeks</td>
</tr>
<tr>
<td>Operating Costs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gowning</td>
<td>✓</td>
<td></td>
<td>RABS Gowning Cost &gt;$300K/yr</td>
</tr>
<tr>
<td>Productivity</td>
<td>✓</td>
<td></td>
<td>RABS reduced productivity</td>
</tr>
<tr>
<td>Changeover</td>
<td>✓</td>
<td></td>
<td>RABS increased changeover time</td>
</tr>
<tr>
<td>Utilities</td>
<td>✓</td>
<td></td>
<td>RABS increased utility cost</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td>similar</td>
</tr>
<tr>
<td>Annual Reval</td>
<td></td>
<td>✓</td>
<td>RABS slightly lower cost</td>
</tr>
<tr>
<td>Env. Monitoring</td>
<td>✓</td>
<td></td>
<td>RABS EM Cost &gt;$1.3 Million</td>
</tr>
</tbody>
</table>
Conclusions –

- RABS may be considered an attractive solution for retrofits of existing lines, but will not replace isolation technology.

- Isolators and RABS will evolve as a pieces of process equipment in and of themselves, with a defined set of functions and requirements.

- RABS utilizes some of the advantages of isolation technology, not all of them.

- With the drive toward improved technology and better solutions for aseptic processing, many RABS stand far short of the capabilities of isolation technology and will likely be used in the future for only specific/narrow applications.