

APV

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

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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

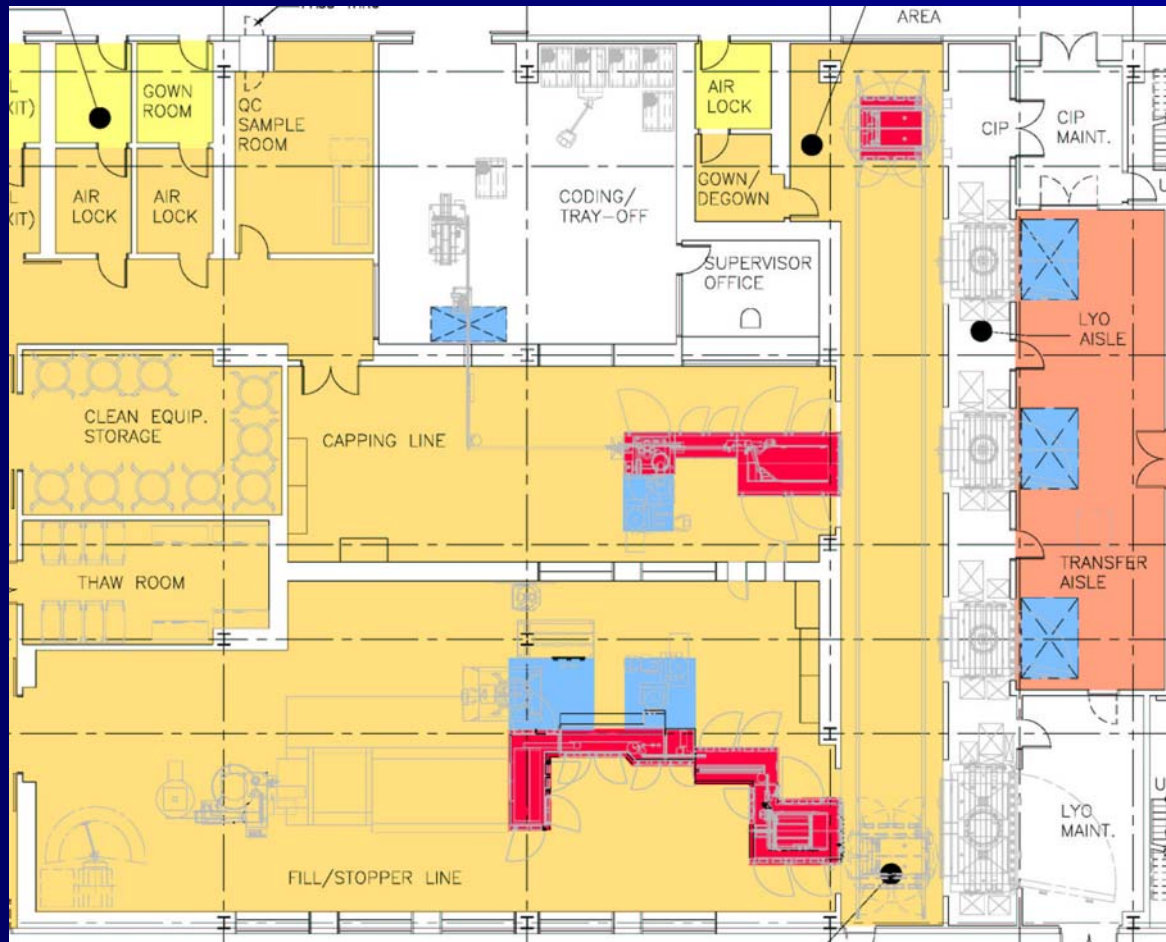
- Secondary – perceived reduction in validation costs and schedule
 - But, no automated disinfection system (H₂O₂ or others)
 - Must still provide data on a non-automated high-level disinfection method of all interior surfaces (sporicidal)
 - Must still provide residue effects and disinfectant removal 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

Area	A	B	C
Sq. Ft.	270	0	2820

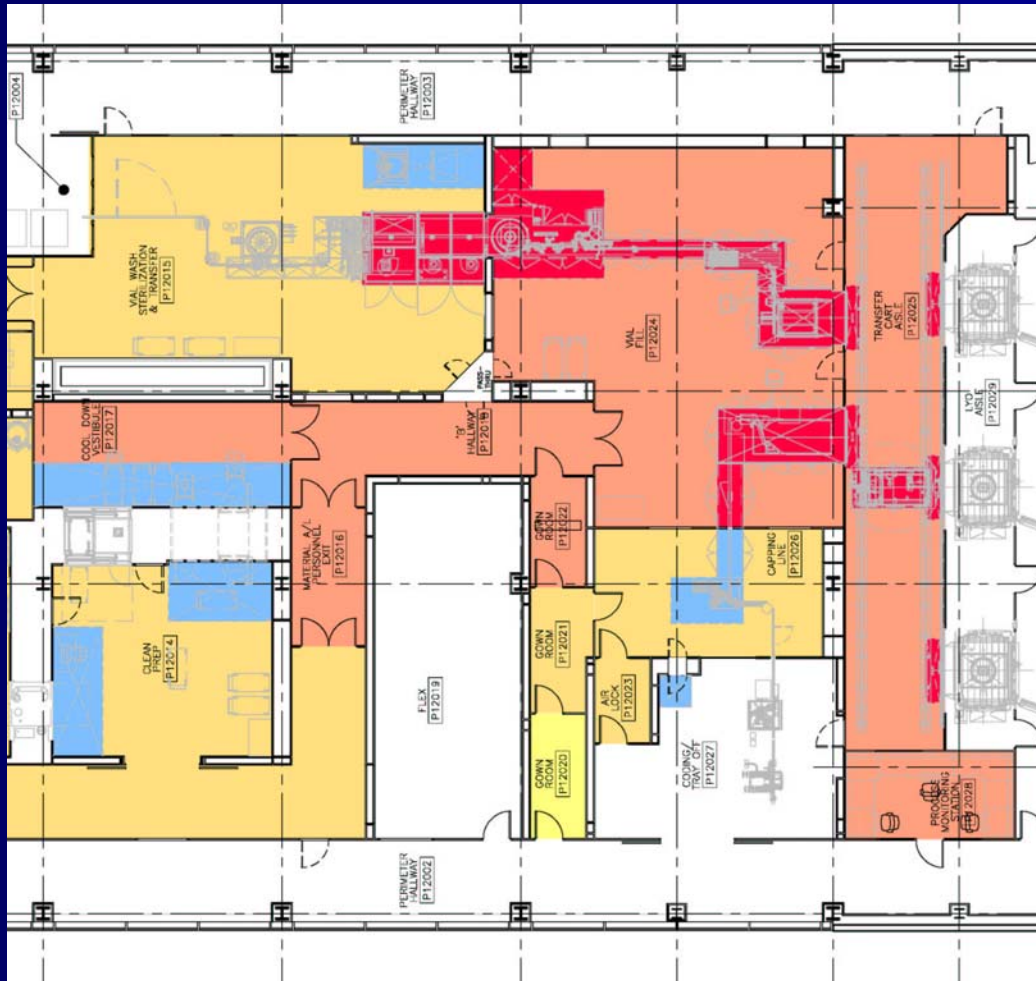


J&J GRADE	CLASSIFICATION				
	JJ-I	JJ-II	JJ-III	JJ-IVa	JJ-IVb
ISO	5	7	B	B (at rest)	unclassified
FORMER US	100	10,000	100,000	100,000 (at rest)	unclassified
EC ANNEX 1 (OPERATIONAL)	A	B	C	N/A	unclassified
EC ANNEX 1 (AT REST)	A&B	C	D	D	unclassified
MINIMUM NUMBER OF AIR CHANGES PER HOUR	90 ft./min.	60	40	25	10
UNIDIRECTIONAL FLOW					

Note: Room Classification Legend based on J&J's "Guideline for Design and Construction of Production Facilities, Manufacturing Operation and Cleanroom", Section 7.0 Attachments and Forms - 7.1 Table 1, "J&J Grade Designation and Equivalency with other Requirements"

Redesigned w/ RABS

Area	A	B	C
Sq. Ft.	418	2972	340



J&J GRADE	ROOM CLASSIFICATION					
	JJ-I	JJ-II	JJ-III	JJ-Iva	JJ-Ivb	JJ-V
ISO	5	7	8	8 (at rest)		unclassified
FORMER US	100	10,000	100,000	100,000 (at rest)		unclassified
EC ANNEX 1 (OPERATIONAL)	A	B	C	N/A		unclassified
EC ANNEX 1 (AT REST)	A&B	C	D	D		unclassified
MINIMUM NUMBER OF AIR CHANGES PER HOUR	90 ft/min.	60	40	25		10
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Current Layout

Area	A	B	C
Sq. Ft.	906	2583	340



ROOM CLASSIFICATION LEGEND						
CLASSIFICATION						
J&J GRADE	JJ-I	JJ-II	JJ-III	JJ-IVa	JJ-IVb	JJ-V
ISO	5	7	8	8 (at rest)		unclassified
FORMER US	100	10,000	100,000	100,000 (at rest)		unclassified
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Cost Analysis – Initial Capital Case #1

	Est. Cost per Sq. Ft.	Iso Area	Iso Cost	RABS Area	RABS Cost
Capital Costs - Equipment			\$ 4,750,000		\$ 2,850,000
A/ISO 5 Area	\$ 900	270	\$ 243,000	906	\$ 815,400
B/ISO 7 Area	\$ 700	0	\$ -	2583	\$ 1,808,100
C/ISO 8 Area	\$ 500	2820	\$ 1,410,000	340	\$ 170,000
Airlock / Gowning Area	\$ 600	400	\$ 240,000	1000	\$ 600,000
Total Estimate		3490	\$ 6,643,000	4829	\$ 6,243,500
Net Savings					\$ 399,500

Cost Analysis – Initial Capital

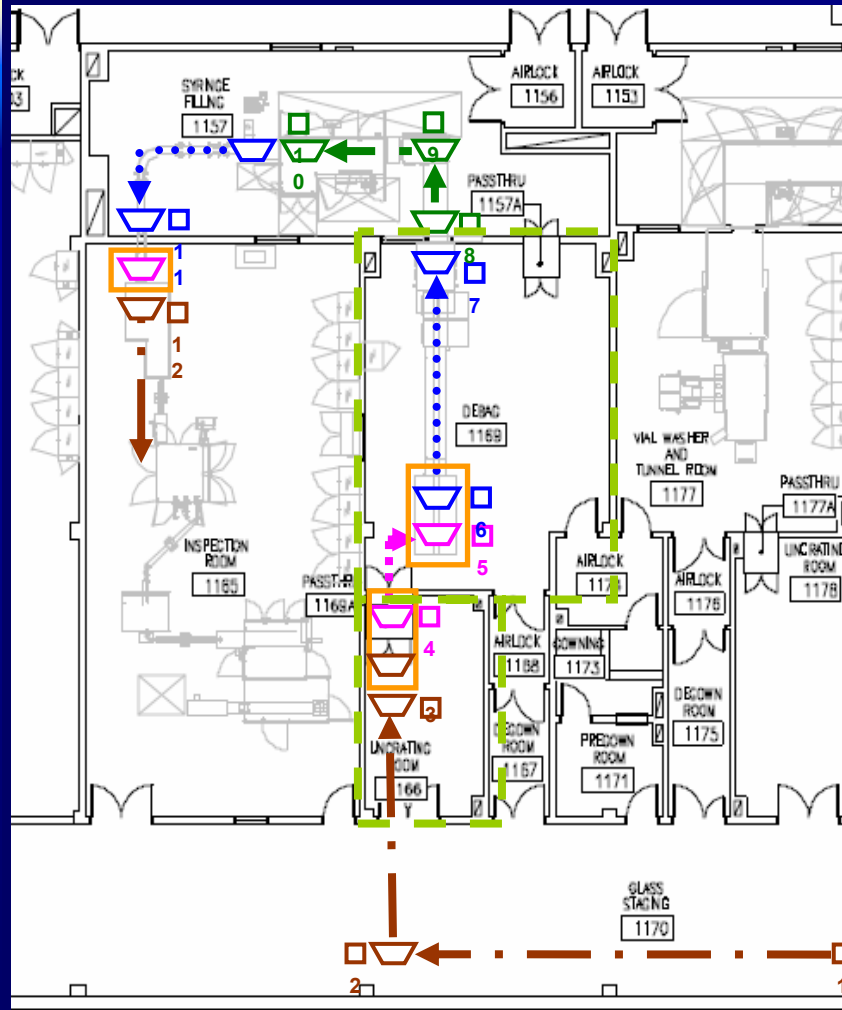
Case #1

- 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)

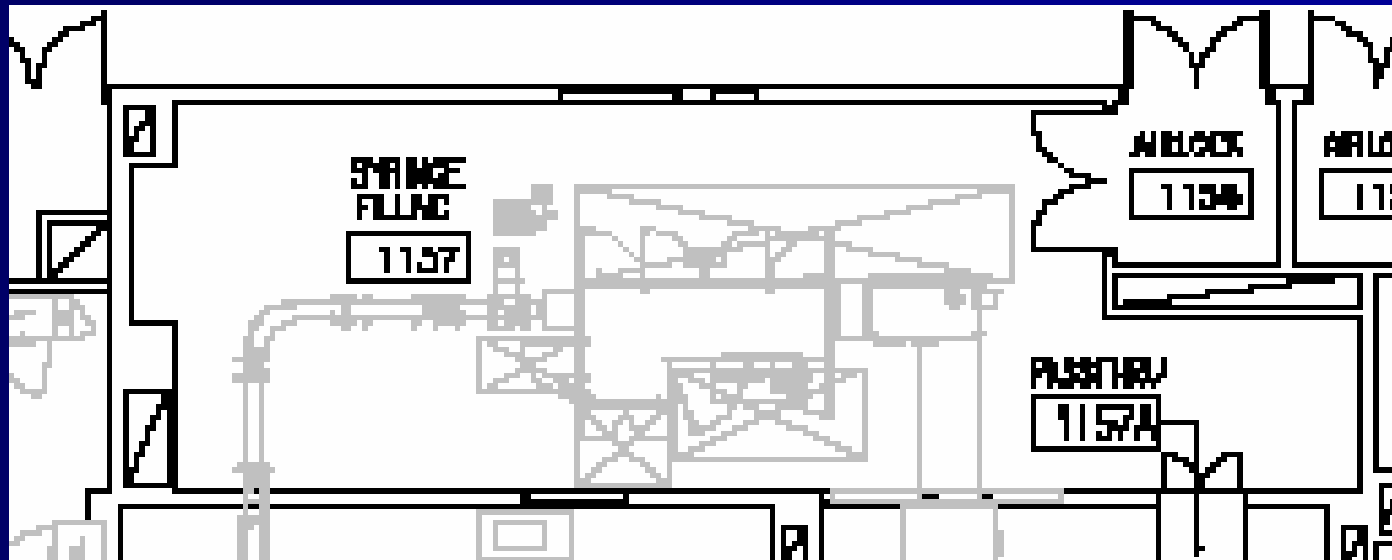
RABS Layout

Area	A	B	C+
ft ²	20	100	870

Isolator Layout

Area	A	B	C+
ft ²	20	0	970

Syringe Line: Filling Room Layout



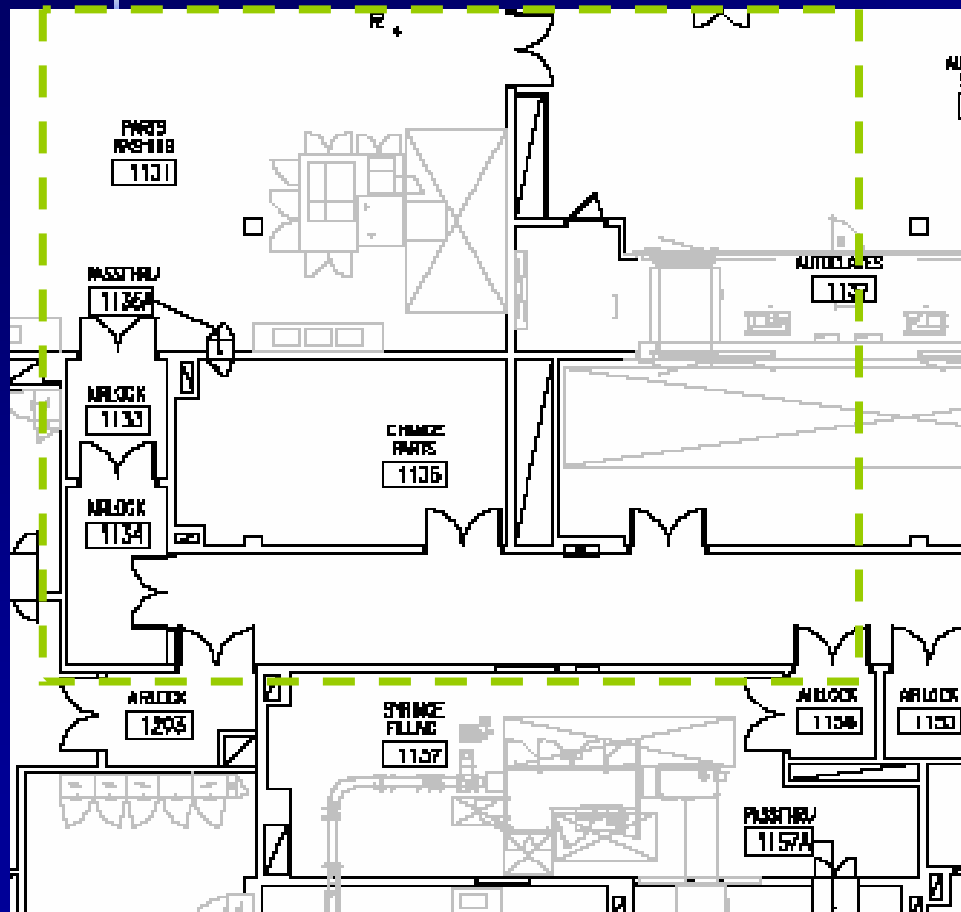
RABS Layout

Area	A	B	C+
ft ²	330	510	N/A

Isolator Layout

Area	A	B	C+
ft ²	110	0	730

Syringe Line: Other Area Layouts



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

RABS Layout

Area	A	B	C+
ft ²	150	800	1500

Isolator Layout

Area	A	B	C+
ft ²	150	N/A	2300

Cost Analysis – Initial Capital

Case #2

	Est. Cost per Sq. Ft.	Iso Area	Iso Cost	RABS Area	RABS Cost
Capital Costs - Equipment			\$ 1,500,000		\$ 750,000
A/ISO 5 Area	\$ 900	170	\$ 153,000	500	\$ 450,000
B/ISO 7 Area	\$ 700	0	\$ -	1460	\$ 1,022,000
C/ISO 8 Area	\$ 500	4000	\$ 2,000,000	2320	\$ 1,160,000
Total Estimate		4170	\$ 3,653,000	4280	\$ 3,382,000
Net Savings					\$ 271,000

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 in 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)

	Sample Freq	Iso Samples	Iso Annual Cost	RABS Samples	RABS Annual Cost
Grade A Area	continuous/ per run	12 air, 40 surface	\$1,040,000	18 air, 60 surface	\$1,560,000
Grade B Area	per run / daily	0	\$ -	8 air, 40 surface	\$ 960,000
Grade C Area	weekly	12 air, 80 surface	\$368,000	7 air, 40 surface	\$188,000
Total Estimate			\$1,408,000		\$2,708,000
Net Cost w/ RABS					**(\$1,300,000)

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

**Represents an cost INCREASE w/ RABS, not savings.

Cost Analysis – Summary

Item	Iso	RABS	Comments
Initial Capital – Barrier Equipment		√	RABS Saves \$1.5-\$2 Million
Initial Capital - Facility	√		RABS Costs >\$1.2-1.5Million
Validation		√	RABS Saves \$100K and 2-4 weeks
Operating Costs:			
Gowning	√		RABS Gowning Cost >\$300K/yr
Productivity	√		RABS reduced productivity
Changeover	√		RABS increased changeover time
Utilities	√		RABS increased utility cost
Maintenance			similar
Annual Reval		√	RABS slightly lower cost
Env. Monitoring	√		RABS EM Cost >\$1.3 Million

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.