



ISPE

The Evolution of Parenteral Facility Design

Mitigating Risk Through Facility Design

Presented by Jason Collins, RA NCARB

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Agenda

- Barrier Technology: Regulatory Perspective
- Definitions: Isolators and RABS
- Historical Technology Perspective
- Choosing a Barrier Technology
- Evolution of Advanced Aseptic Facility Design

Regulatory Perspective



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Regulatory Perspective

*The single greatest source of **risk** in aseptic processing is personnel-related contamination that can be addressed by incorporating the following into aseptic line design:*

- **Separation** of the external clean room environment from the aseptic processing line through the use of Isolators or closed RABS . The movement toward closed systems has been an important advance to secure patient safety.
- **Automation** and integration of aseptic line operations to eliminate manual interventions wherever possible. As automation increases, the cumulative risk of production operators as vectors of contamination in the aseptic process will diminish.

Regulatory Perspective

*“Some aseptic operations that are unnecessarily vulnerable to contamination hazards remain in the industry. Antiquated design concepts continue to be perilously open to the adverse influence of external variables. These older, open aseptic processing systems (including open RABS) will continue to receive **extra** regulatory attention because so many variables must be properly controlled to ensure consistent contamination prevention. FDA inspections have found noncompliant facilities that allow a major and persistent risk of sporadic contamination... ultimately these firms realized the need for very extensive corrective actions to eliminate fundamental design flaws.”*

Regulatory Perspective

Design of personnel and material flows, including transitions and transfers, should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, containers, closures or the surrounding environment.

Personnel transitions have been redefined in the recent revisions to the EU Annex 1 aseptic guidance document:

- Outdoor clothing should not be brought into change rooms leading to Grade C (ISO 8) or higher classified rooms.
- Grade C (ISO8) requires hair covers, non-particulating trouser suit, gathered at the wrists with a high neck, and shoe covers.

Regulatory Perspective

2012 ISPE Tampa Conference

- **Q: Are submittals for traditional based aseptic facilities being seen by the agencies?**

We generally expect to see barrier technologies used. There are very limited exceptions, such as the classic LAF hood for very simple operations. But these operations must, nonetheless, be carefully designed and controlled to protect the exposed sterile product throughout all manipulations. Some of the traditional facilities operate on the edge of failure. FDA scrutiny will be more intense for traditional versus barrier facilities.

Regulatory Perspective

2012 ISPE Tampa Conference - *Continued*

- You rarely, if ever, see isolators in warning letters. We have, however, seen isolators fail media fills. Any operation can fail if a firm does not control and maintain it well enough.
- Every time a RABS door is opened, a deviation should be written.
- If you open the doors of a closed RABS, you must scrub the rest of the batch.
- No opened doors during filling operation is a 'closed RABS'.
- New large volume Pharma lines should be Isolator or Closed RABS.
- Putting plexiglass around an old filling line is not a RABS.
- All doors shall open into unidirectional ISO 5 air supply.
- New generation filling machines that require fewer interventions should be used.

Definitions: Isolators & RABS

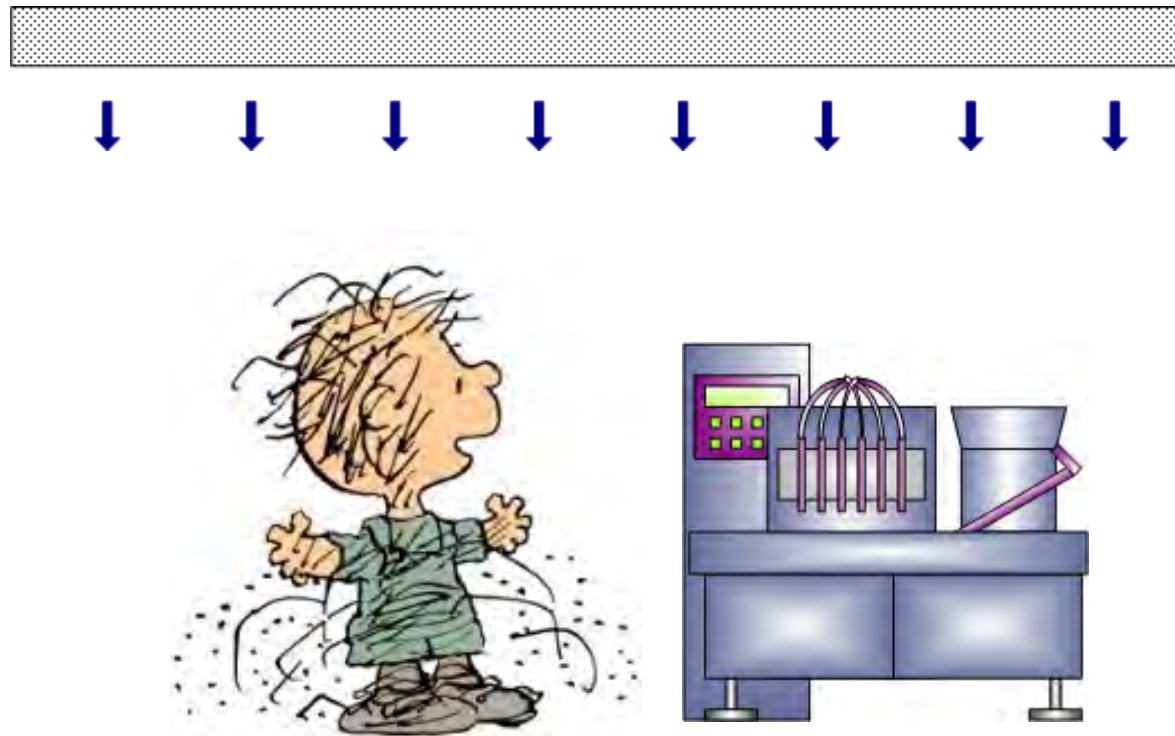


Aseptic Risk Reduction

- Operator(s) = Particulate Generators

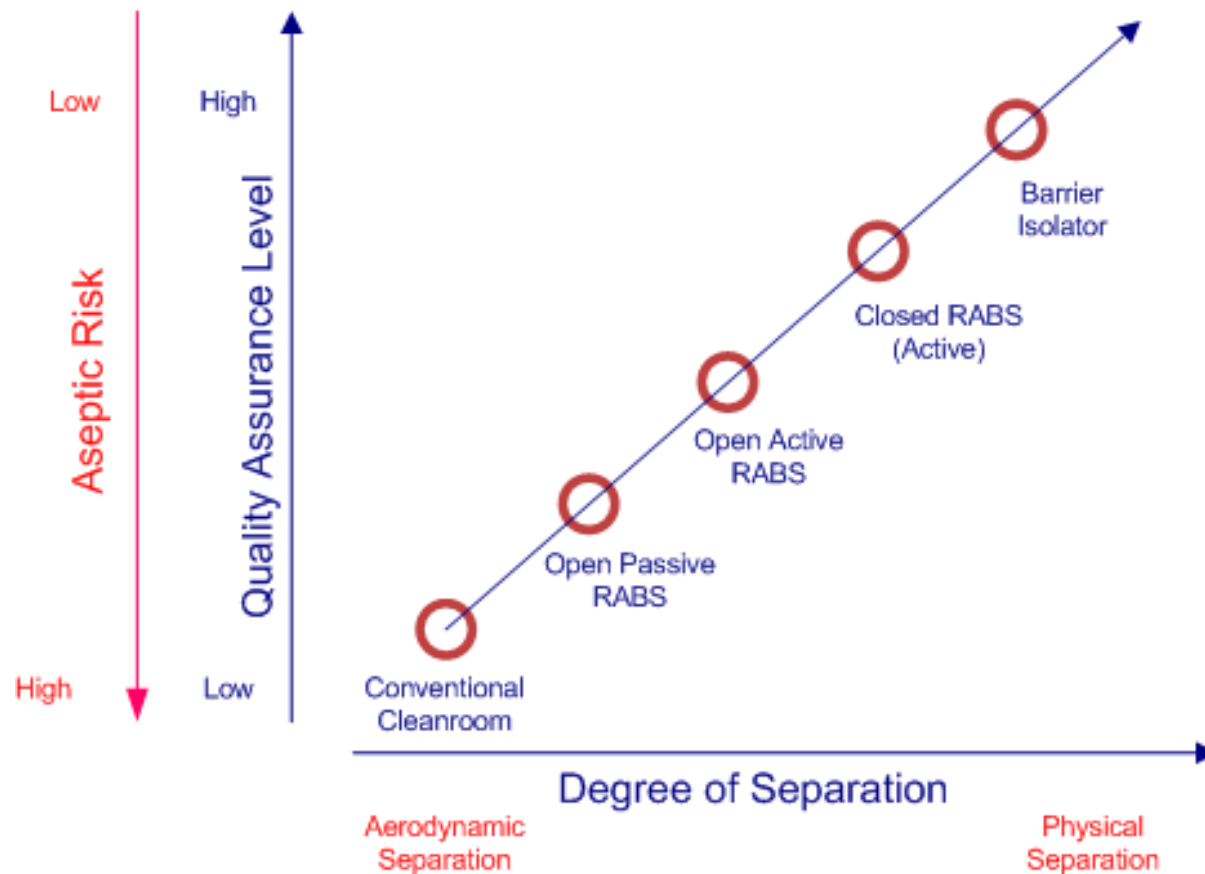


Aseptic Risk Reduction



Conventional Clean Room Technology

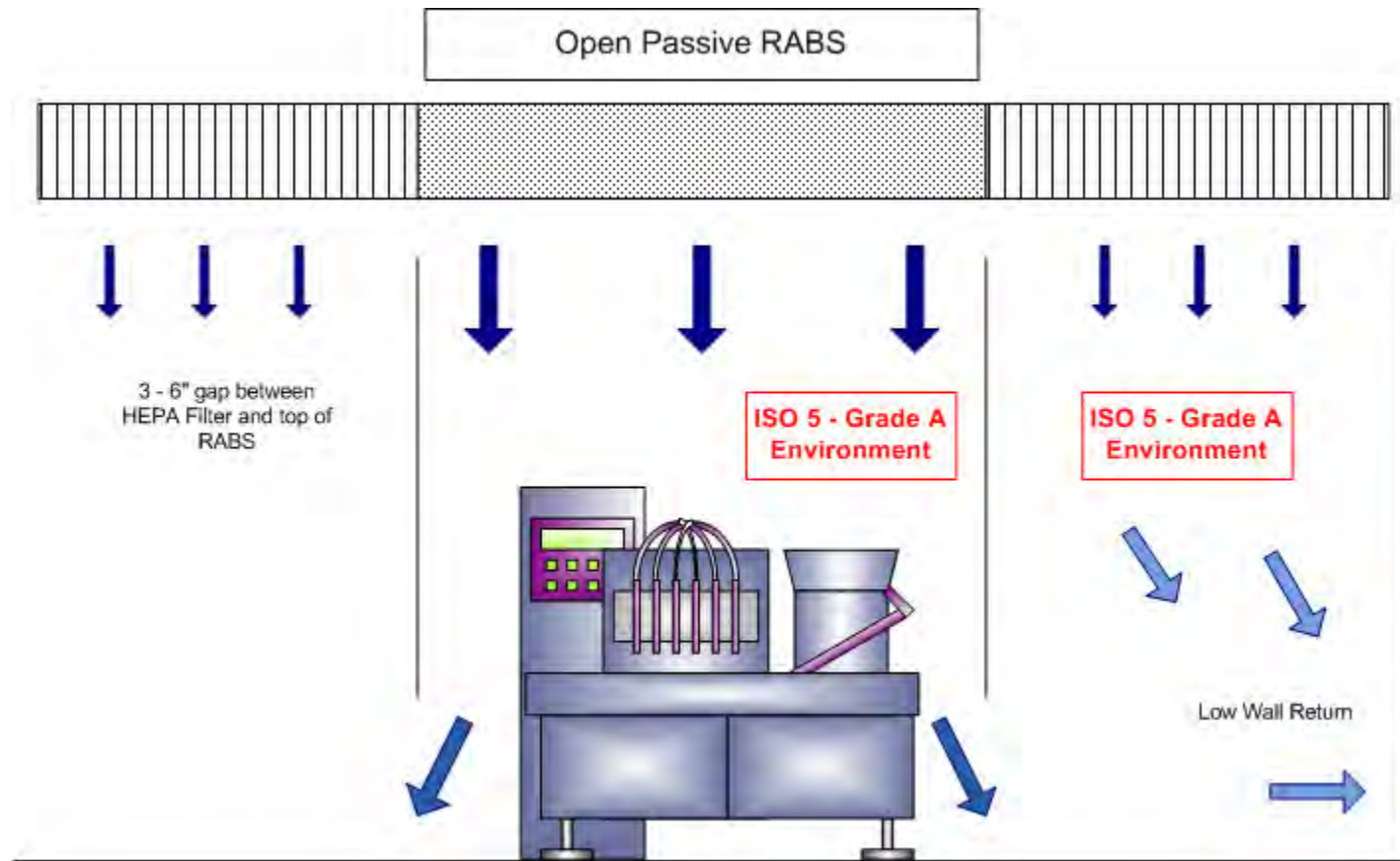
Aseptic Risk Reduction



Aseptic Risk Reduction - RABS

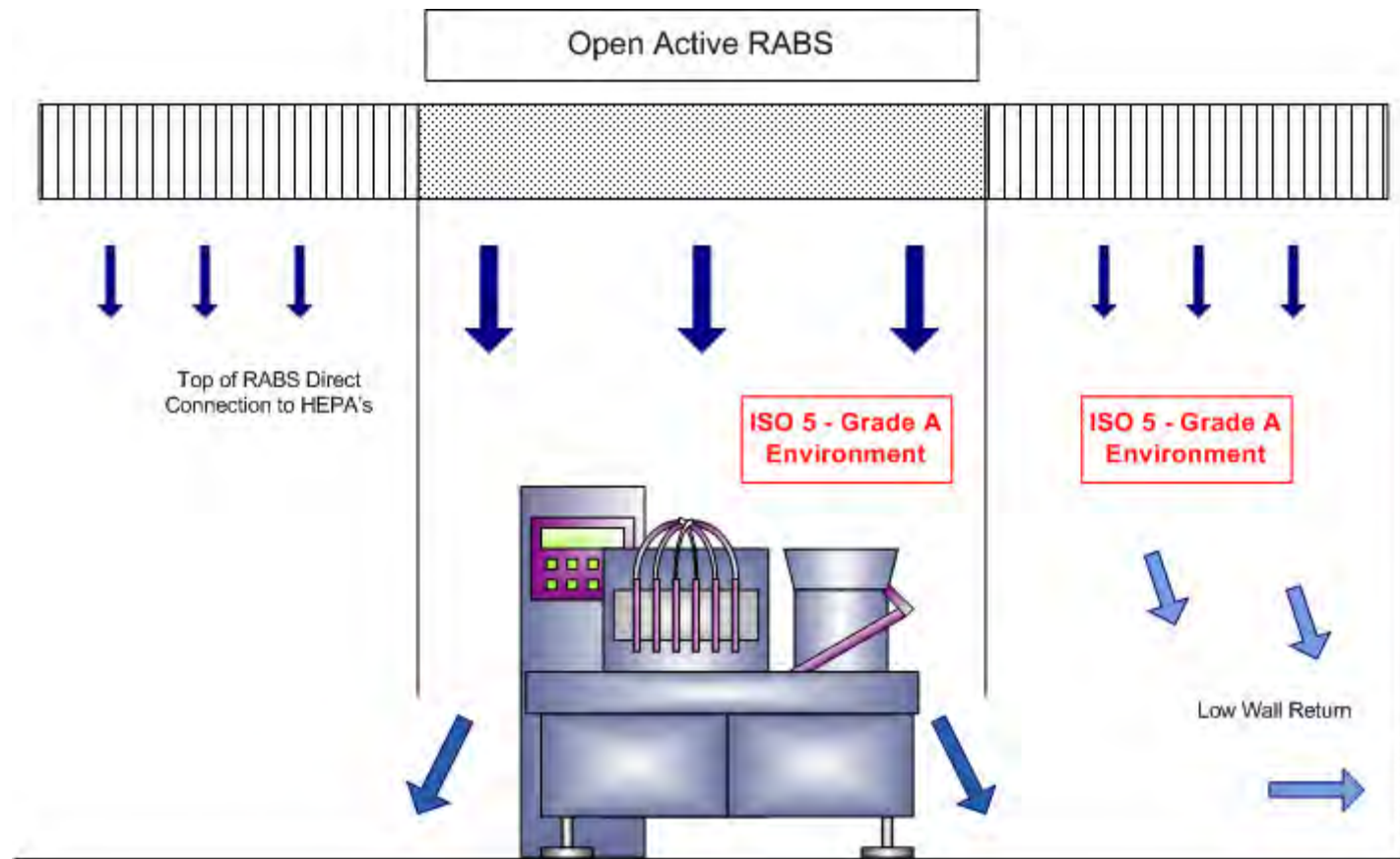
- Restricted Access Barrier System
- Types
 - 1) Open - Any Barrier System where the doors are opened for interventions during filling operations.
 - 2) Open/Passive
 - 3) Open/Active
 - 4) Closed - A Barrier System that fully encloses the filling operations and re-circulates the air internally.
 - 5) Locked - Any Barrier System where the doors remain closed for all interventions during filling operations.

Aseptic Risk Reduction - RABS



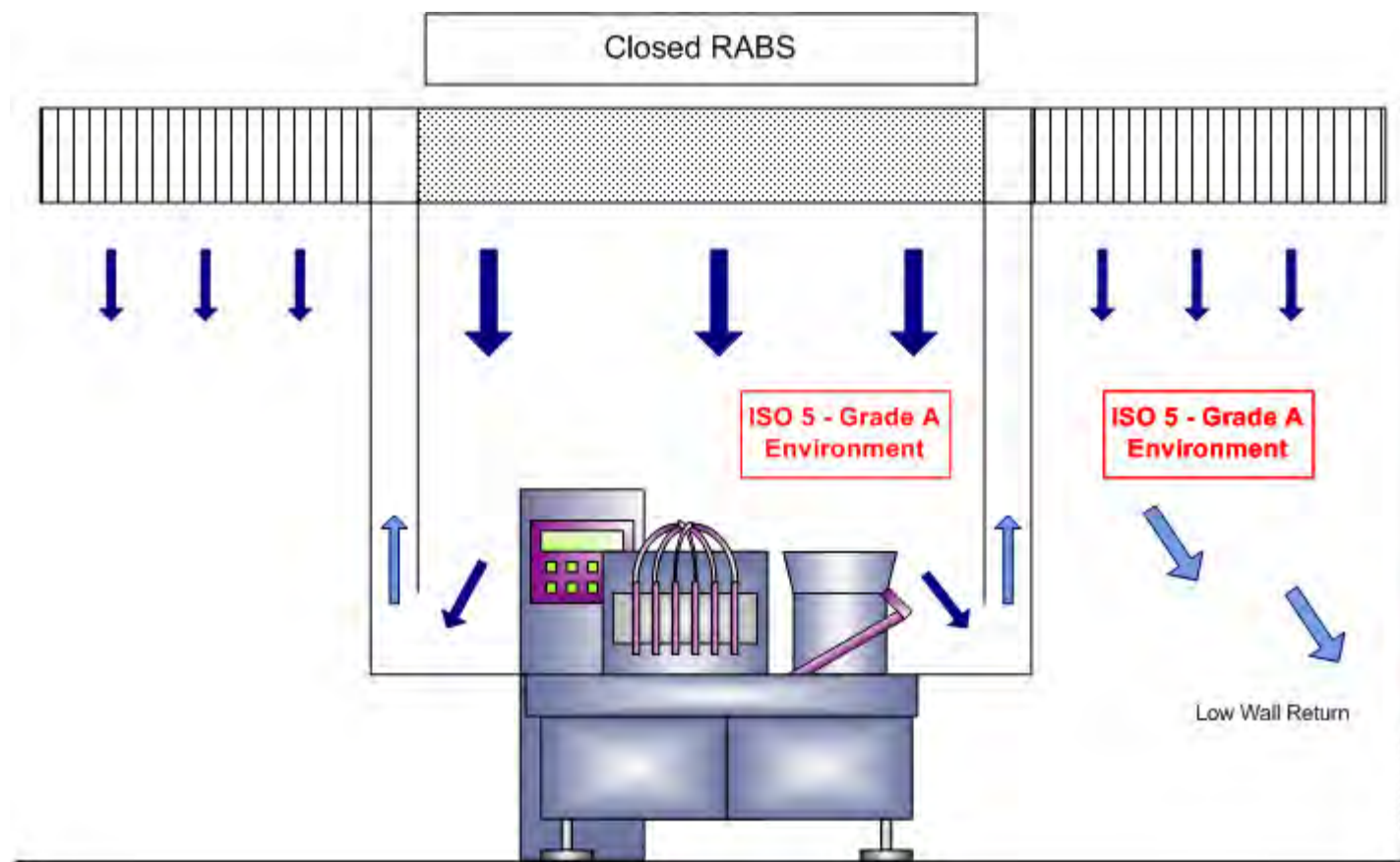
A Barrier System where the air is provided by a LAF in the ceiling and has an open bottom that returns the air to the room.

Aseptic Risk Reduction - RABS



A Barrier System with an integral LAF and open bottom that returns the air to the room.

Aseptic Risk Reduction - RABS

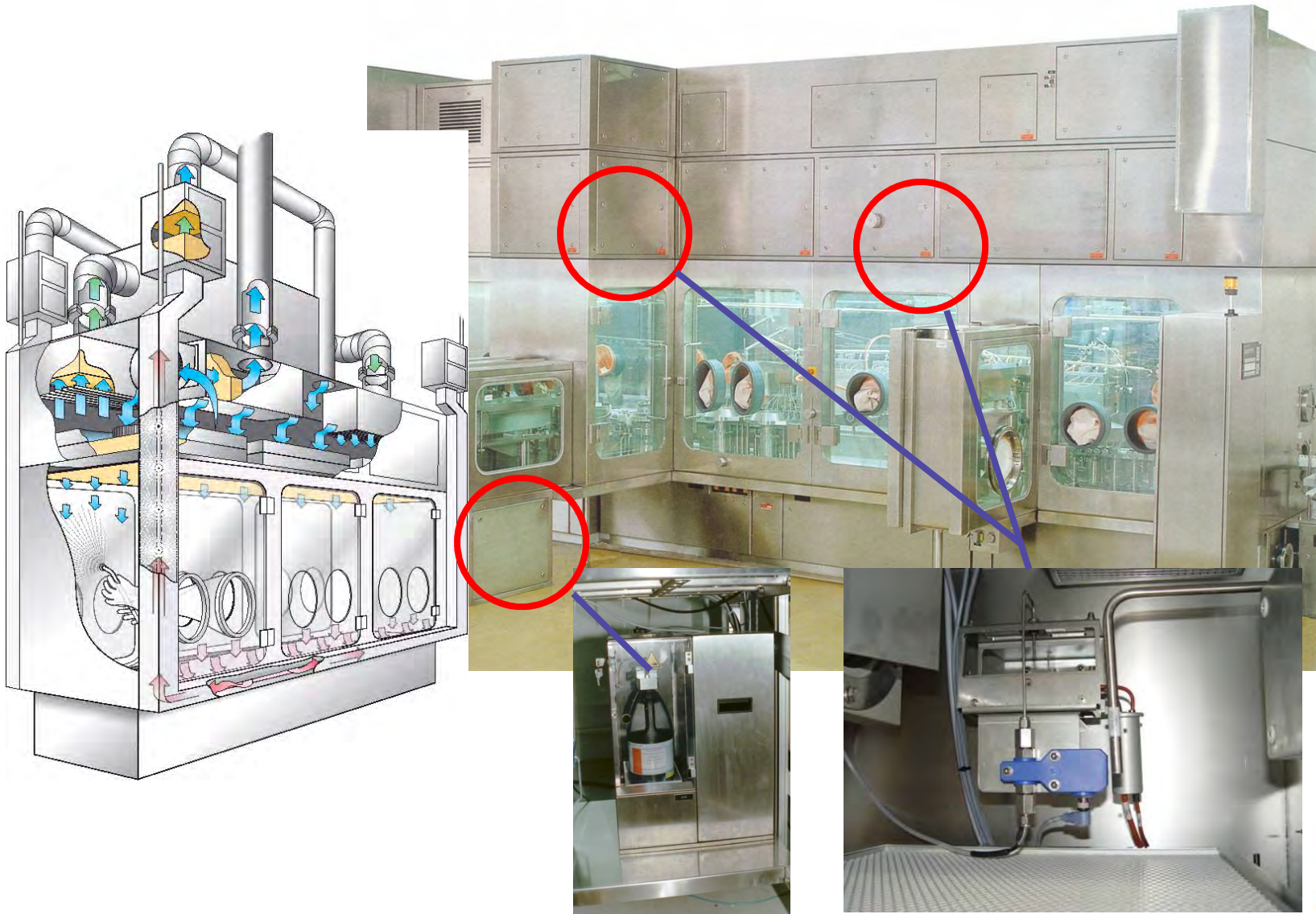


A Barrier System that fully encloses the filling operations and re-circulates the air internally.

Aseptic Risk Reduction - Isolators

- A Closed Barrier System that utilizes automated chemical sanitization versus manual cleaning.
- Materials are transferred into the isolator via closed systems such as a Rapid Transfer Port (RTP) or a SARA (SAfe RApid Transfer Box).

Isolator Sanitization



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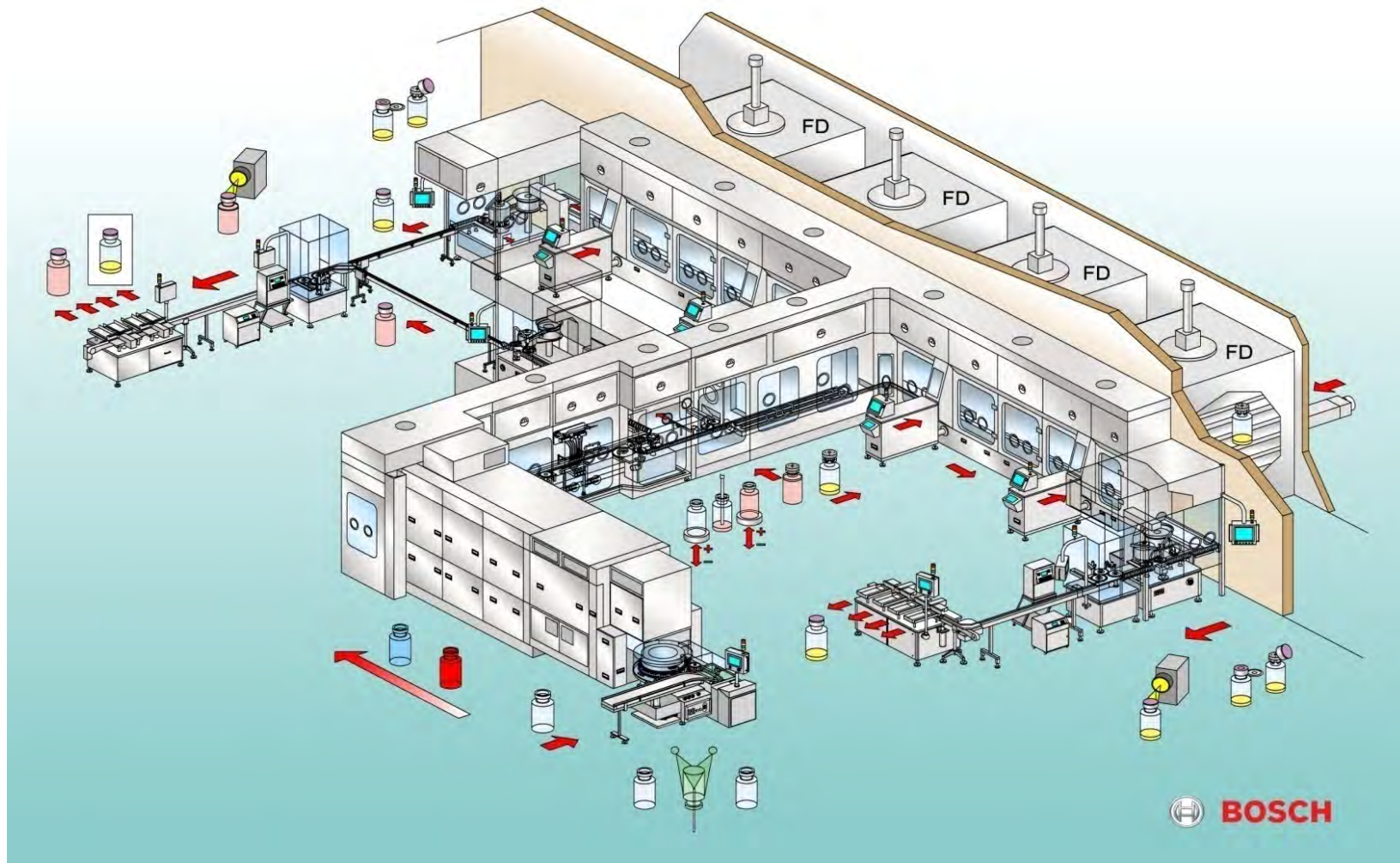
Isolated Filling Lines



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Isolated Filling Line - Isometric



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Historical Technology Perspective



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Historical Perspective

- Traditional Clean Room Development
 - Operator Interventions & Contamination Risk
 - High Operating Costs
- LUMS Isolators
 - Validation Issues
 - Extended VHP Cycle
- Restricted Access Barrier System (RABS)
 - Reduced GMP Risk with Higher Costs
- 21st Century Isolators
 - Greatly Reduced GMP Risk at Lower Costs

Traditional Aseptic Clean Room and Open RABS

- Grade A/B, ISO 5/7 Suite Design
- Full 'Space Suit' Gowning
- Issues:
 - Operator Interventions
 - Operator Contamination
 - Re-producible Cleaning
 - Expensive to Operate
 - Difficult Aseptic Transfers

Closed RABS Technology

- Add a Barrier System to Limit Operator Interventions
- Issues:
 - Still Grade A/B, ISO 5/7 Environment
 - Most Expensive to Construct
 - Still Expensive to Operate
 - Defining Sanitization Process
 - Validating Laminar Air Flow

Isolation Technology

- Delayed Introduction Due to Resistance to New Technology and 18-Hour VHP Cycle
- Current VHP Cycle as Low as 2 Hours
- Ease of Aseptic Product/Material Transfer
- Ease of Gowning and Aseptic Operating Techniques
- Operator Segregation from Exposed Product
- Entire Suite Grade C/ ISO 8
- Lowest Life Cycle Costs
- Smaller Aseptic Suite
- Automated, Reproducible Sanitization

Choosing a Barrier Technology

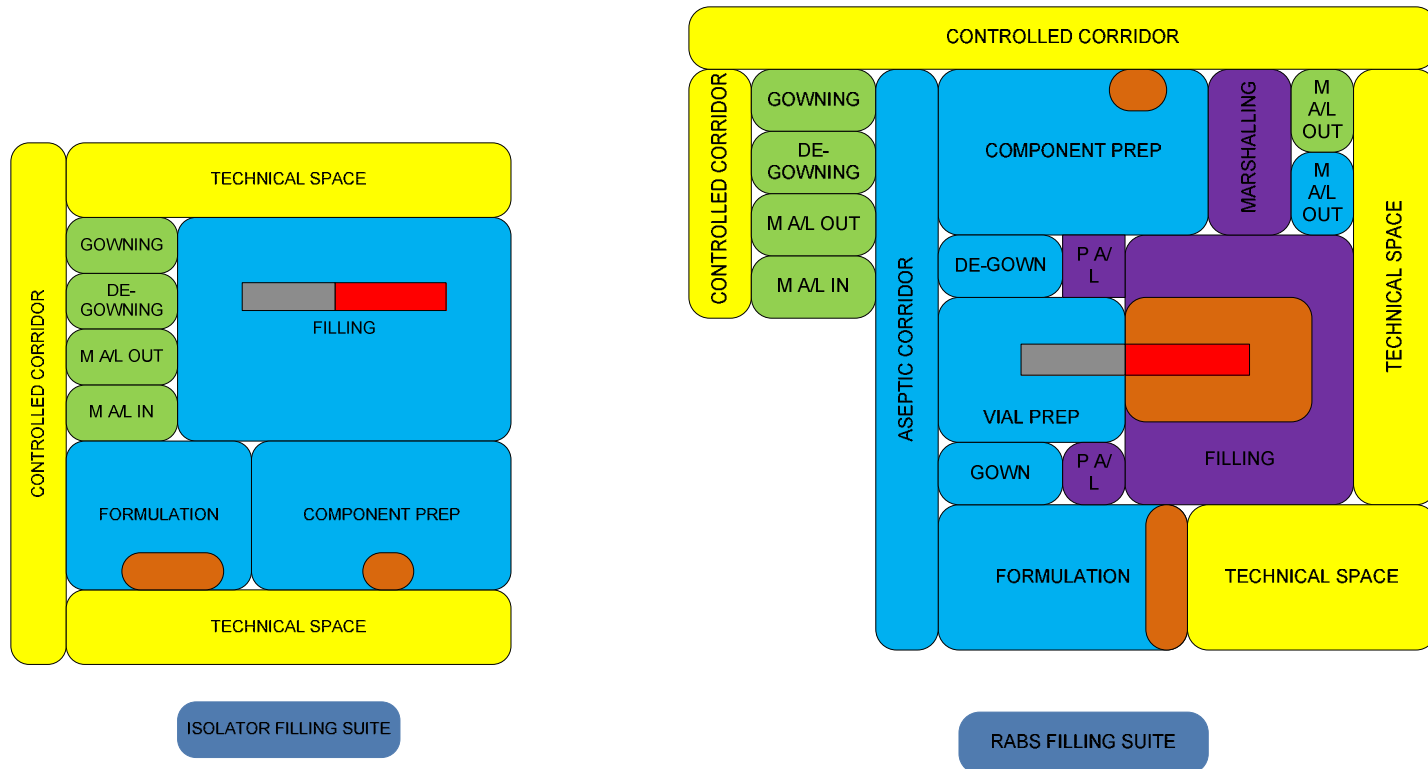


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ISOLATOR vs. RABS

Facility Size/Cost Impact



Isolator

RABS/Traditional

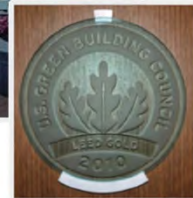
ISOLATOR vs. RABS Facility

Size/Cost Impact

ITEM	SPACE	RABS TECHNOLOGY				ISOLATOR TECHNOLOGY			
		EU GRADE	\$/SF	SF	\$	EU GRADE	\$/SF	SF	\$
	FILLING LINE	A			IN EQUIP	A			IN EQUIP
1	FILLING ROOM	A SUPPLY	1100	500	550000	N/A			
2	FILLING ROOM	B	650	650	422500	C	450	1248	561600
3	FORMULATION	B	650	765	497250	C	450	300	135000
4	COMPONENT STAGING	B	650	900	585000	N/A			
5	CAPPING	B	650	550	375500	INCL			
6	B GOWN/DE-GOWN	B	650	900	585000	N/A			
7	B M A/L	B	650	1000	650000	N/A			
8	FLEX SUITE	B	650	1500	975000	C	450	1170	526500
9	COMPONENT PREP	C	450	2500	1125000	C	450	990	445500
10	TANK WASH/STORE	C	450	450	202500	C	450	210	94500
11	VIAL WASH/DRY	C	450	550	247500	INCL			
12	CLEAN PARTS STORE	N/A				C	450	702	315900
13	TERM STERILE	D	300	400	120000	C	450	140	63000
14	C GOWN/DE-GOWN	C	450	1200	540000	N/A			
15	C M A/L	C	450	1200	540000	N/A			
16	C CORRIDOR	N/A				C	450	1000	450000
17	D CORRIDOR	D	300	5000	1500000	N/A			
18	D GOWN/DEGOWN	N/A				D	300	320	96000
19	D M A/L	D	300	450	135000	D	300	320	96000
20	INSPECTION	D	300	750	225000	CNC	250	580	145000
21	PACKAGING	D	300	810	243000	CNC	250	810	202500
22	INPROCESS STAGE	D	300	700	210000	CNC	250	720	180000
23	CNC CORRIDOR	N/A				CNC	250	1075	268750
24	LOCKERS	D	300	750	225000	CNC	250	600	150000
25	TOILETS	UC	200	500	100000	UC	200	480	96000
26	SHOWERS	UC	200	600	120000	N/A			
27	PROCESS MECHANICAL	UC	200	2400	480000	UC	200	2475	495000
28	PROCESS UTILITIES	UC	200	1065	213000	UC	200	1065	213000
29	UC CORRIDOR	UC	200	1650	330000	UC	200	3200	640000
30	TOTALS			27740	11196250			17405	5174250

HVAC/ Energy Impact

- Air Volume
 - ISO 5/ Grade A: 600 ACPH
 - ISO 7/ Grade B: 65 ACPH
 - ISO 8/ Grade C: 20 ACPH
- RABS Air Flow Issues
- Room/Isolator Integration
 - Make-up Air Options
 - Ducting the Isolator
- Energy Savings / GREEN



Operating Impact

- Gowning Materials
- Gowning Time
- Environmental Monitoring
 - Viable
 - Non-Viable
 - Micro-Lab
- Staffing
 - Production
 - Laboratory



Initial Capital Cost Impact

- Isolator Versus C-RABS
 - Isolator Filling Suites Typically Cost 50% of C-RABS Filling Suites
 - Isolators Typically Cost 25% More Than C-RABS
 - Isolator Projects Typically Cost Less Than C-RABS Projects

Initial Capital Costs- Example

ITEM	UNIT COST	ISOLATOR AREA	ISOLATOR COST	RABS AREA	RABS COST
GRADE A/ ISO 5	1100			240	154,000
GRADE B/ ISO 7	650			1768	1,149,200
GRADE C/ ISO 8	450	1658	746,100	360	162,000
GRADE D/ CNC	250	2330	557,500	1620	405,000
UNCLASSIFIED	200		equal		equal
DOCK RENOVATION	125		equal		equal
FORMULATION RENO	125		equal		equal
OH&P	0.15		195,540		280,530
FACILITY SUB-TOTAL			1499140		2,150,730
FILLING LINE	1,600,000		1,600,000		1,600,000
ISOLATOR	1,989,072		1,989,072		
CLOSED RABS	1,367,466				1,367,466
INSPECTION/LABEL			equal		equal
SECONDARY PACKAGE			equal		equal
EQUIPMENT SUB-TOTAL			3,589,072		2,967,466
START UP	0.02		71,780		59,340
CQV	0.04		143,560		118,680
DESIGN	0.07		105,000		150,500
SERVICE SUB-TOTAL			320,340		328,520
TOTAL CAPITAL			5,408,552		5,446,716

Operation Expense Impact

- Gowning Materials
- Gowning Labor
- Environmental Monitoring
- HVAC Savings
- Utility Savings
- Manufacturing Labor
- Cleaning Labor

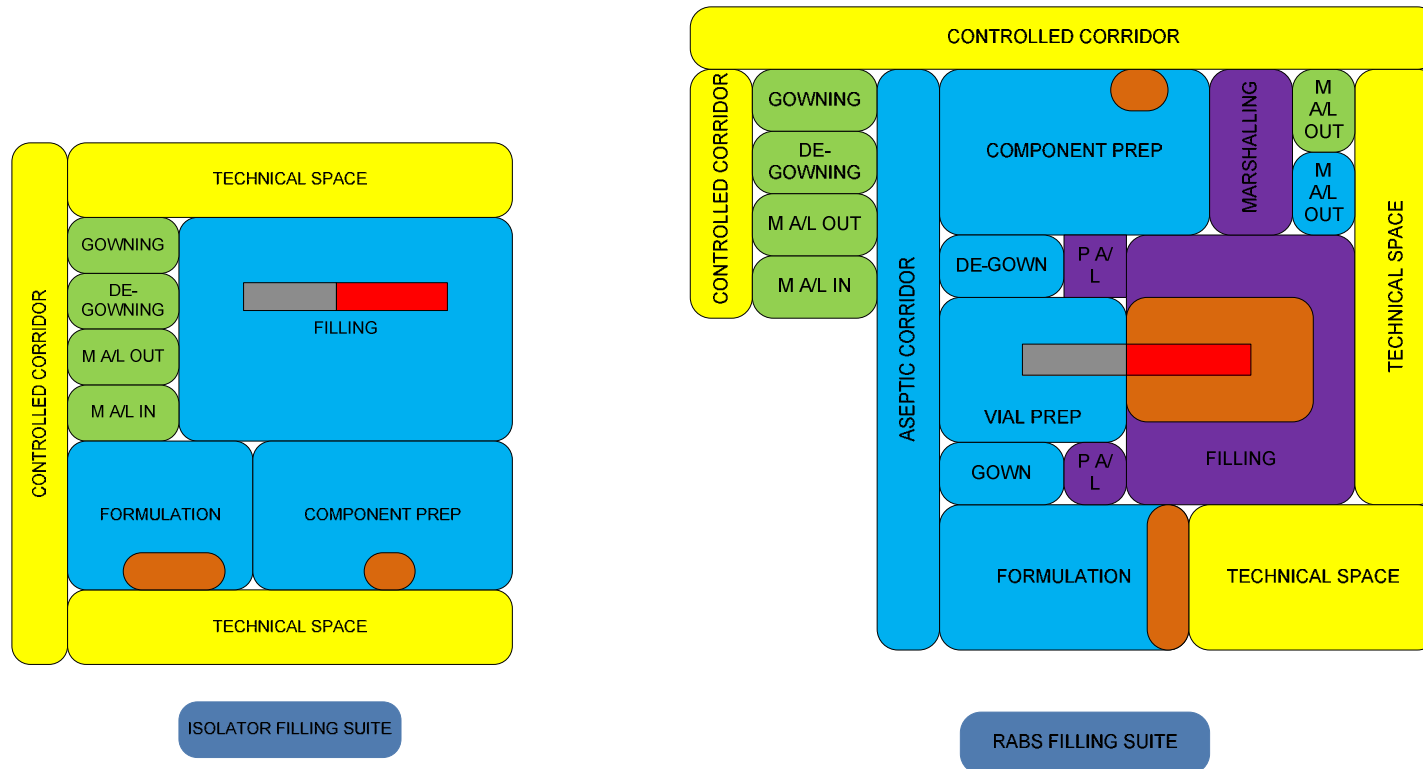
Operation Expense - Example

ITEM	UNIT COST	UNITS/YEAR	ISOLATOR	UNIT COST	UNITS/YEAR	RABS
FACILITY Annualized	1,500,000	0.033	49,500	2,150,000	0.033	70,950
EQUIPMENT Annualized	3,589,000	0.1	358,900	2,967,466	0.1	296,746
GOWN MATERIALS	40.2	690	27,738	168.6	2070	349,002
CLEANING MATERIALS	1860	46	85,560	1860	230	427,800
GOWNING LABOR	63	230	14,490	252	230	57,960
CLEANING LABOR	350	46	16,100	350	230	80,500
MFG LABOR NET	X	X	X	350	230	80,500
HVAC COSTS NET	X	X	X			35,576
TOTAL COST			552,288			1399034
						850,000

ASSUMPTIONS:

1. 230 FILL DAYS PER YEAR
2. STAFF OF 3X3 CHANGES PER DAY
3. 10-YEAR EQUIPMENT LIFE
4. 30-YEAR FACILITY LIFE

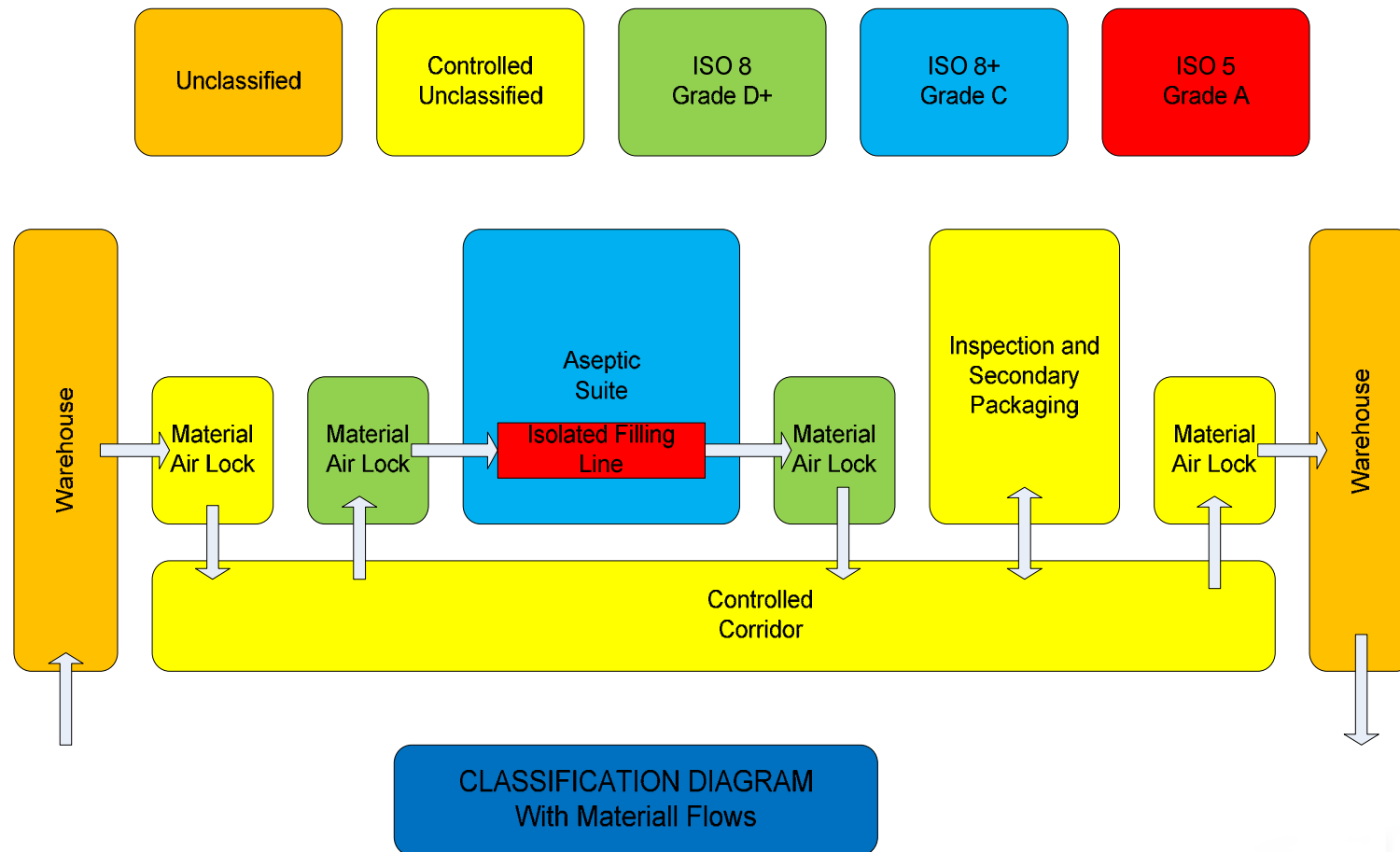
Evolution of Advanced Aseptic Facility Design



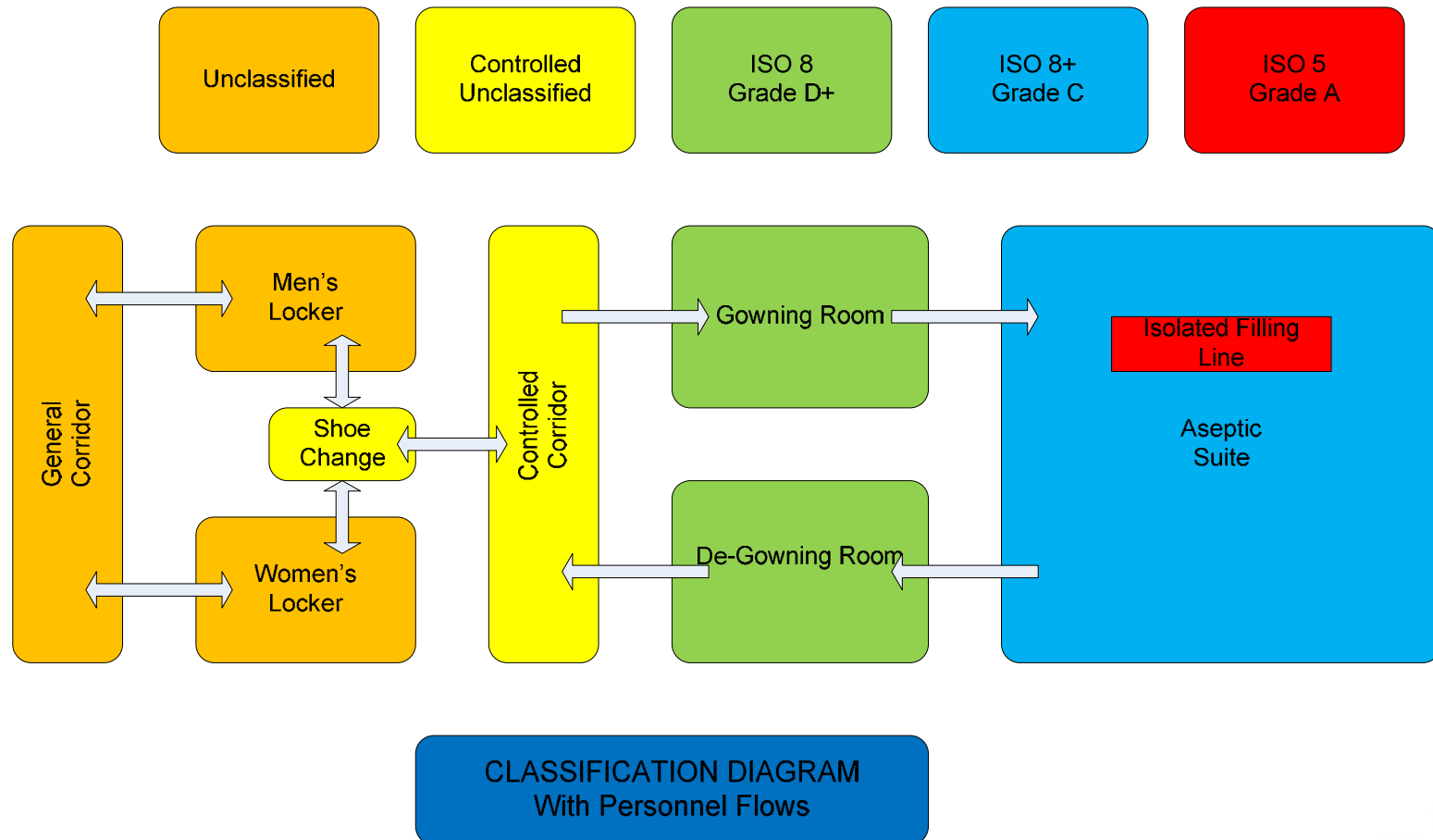
Isolator

RABS/Traditional

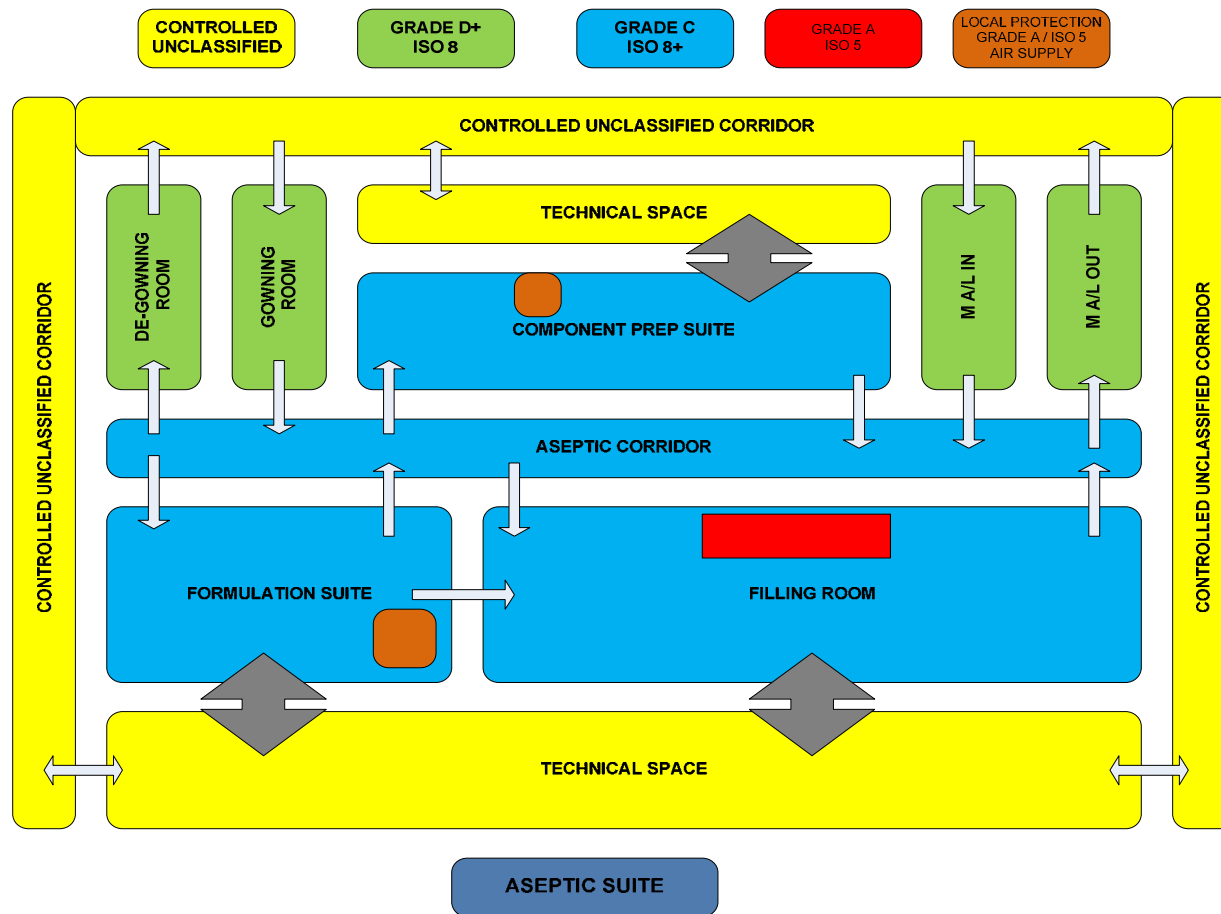
Classification Diagram With Material Flows



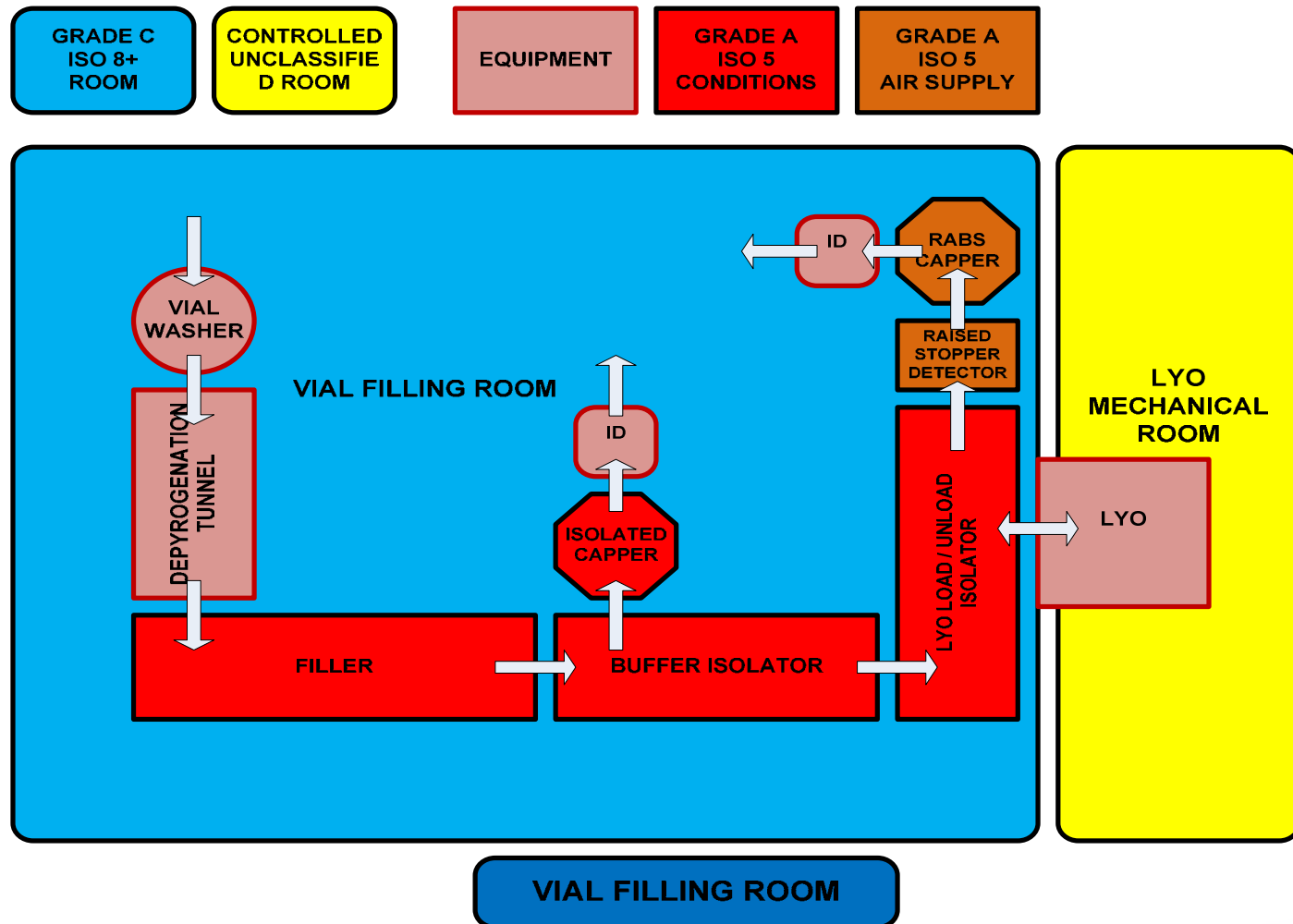
Classification Diagram With Personnel Flows



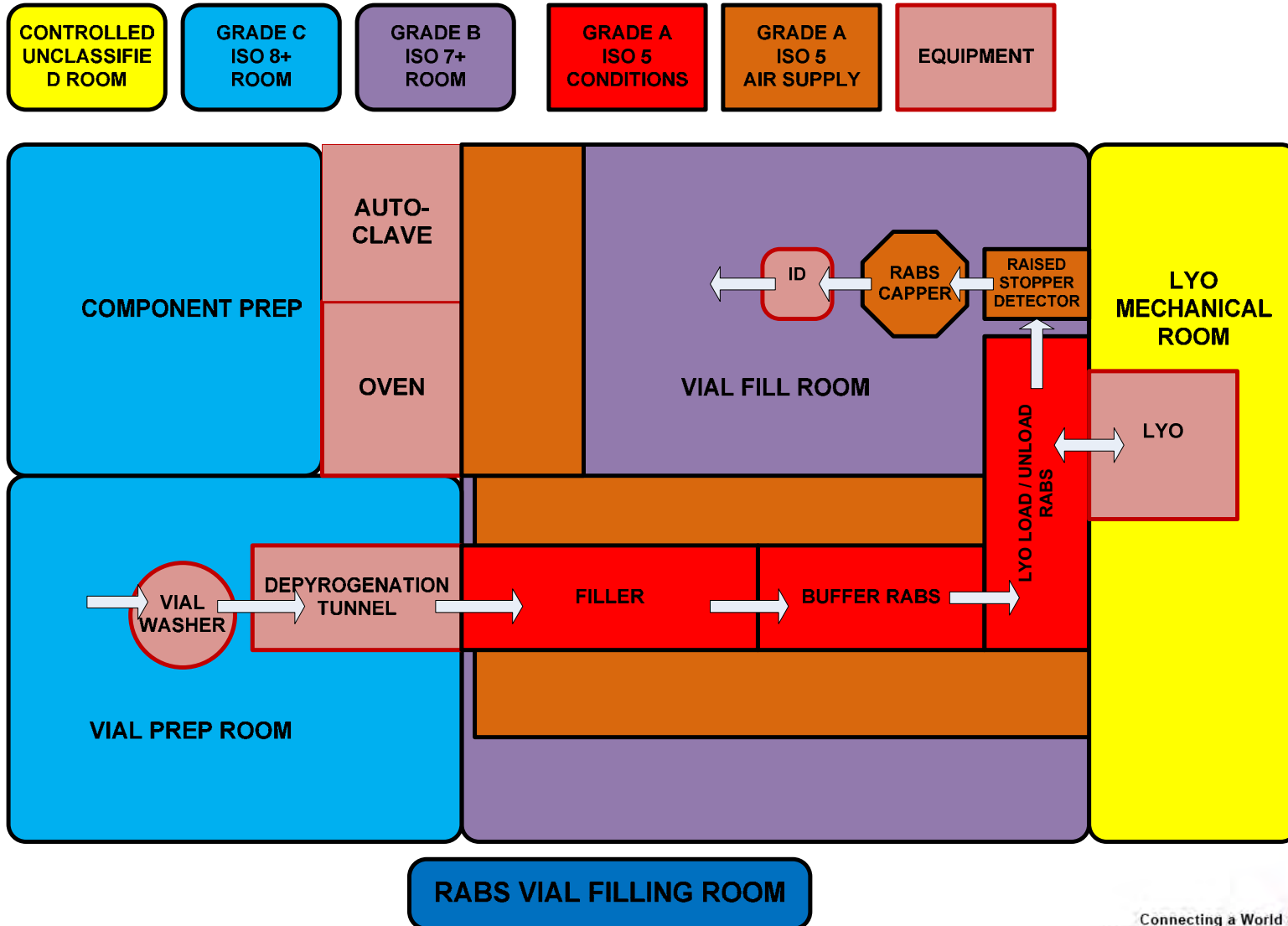
Aseptic Suite



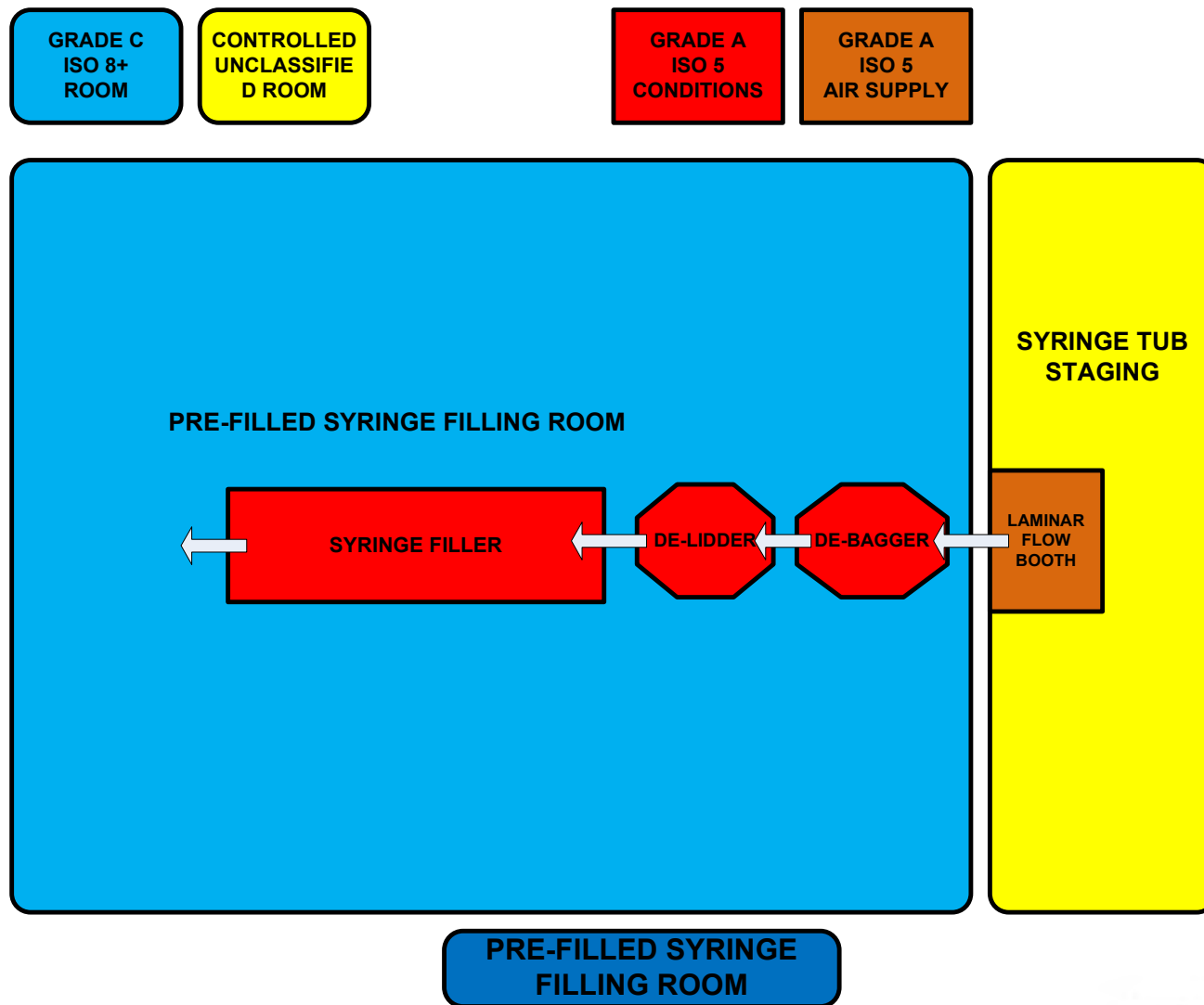
Vial Filling Room



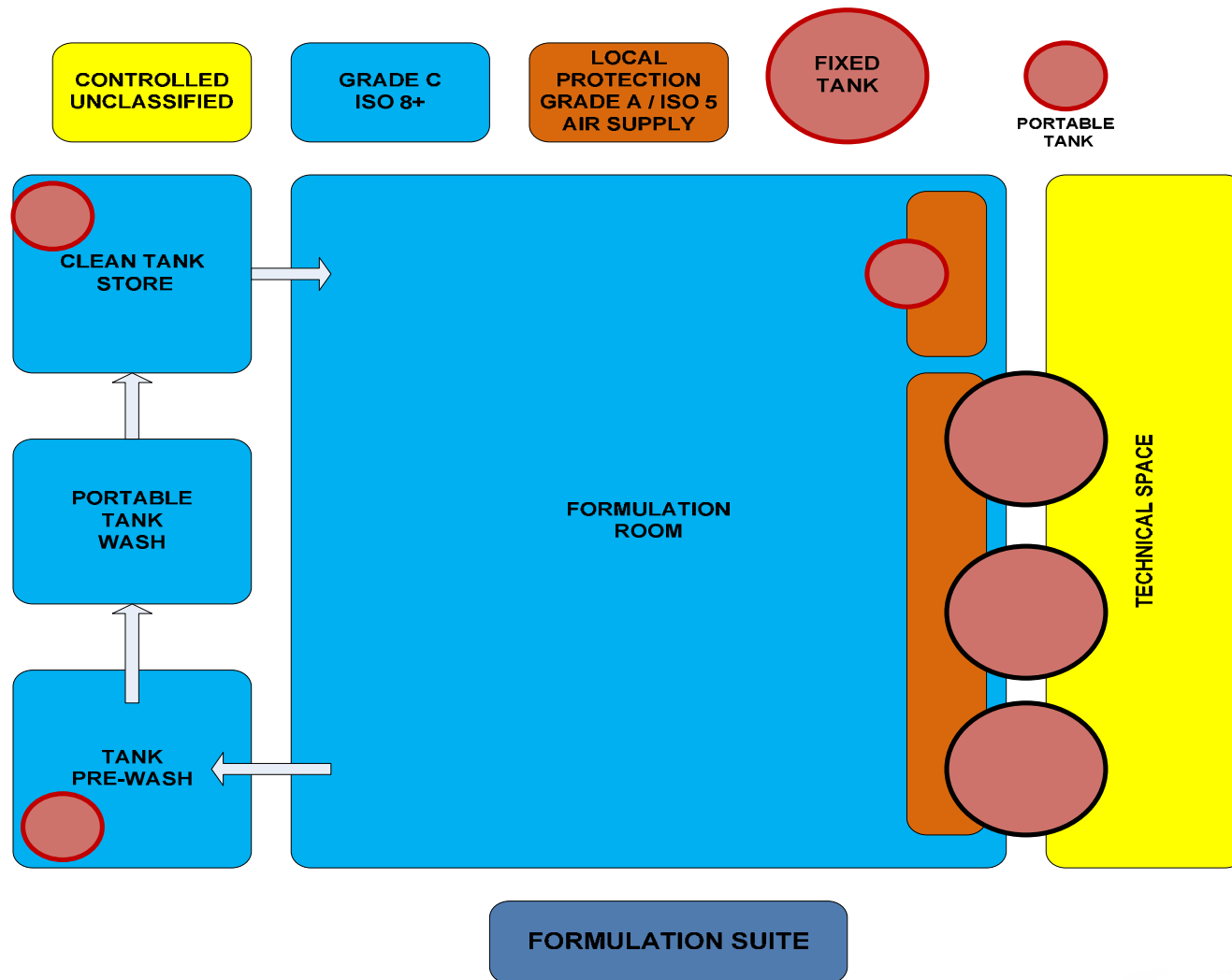
RABS Vial Filling Room



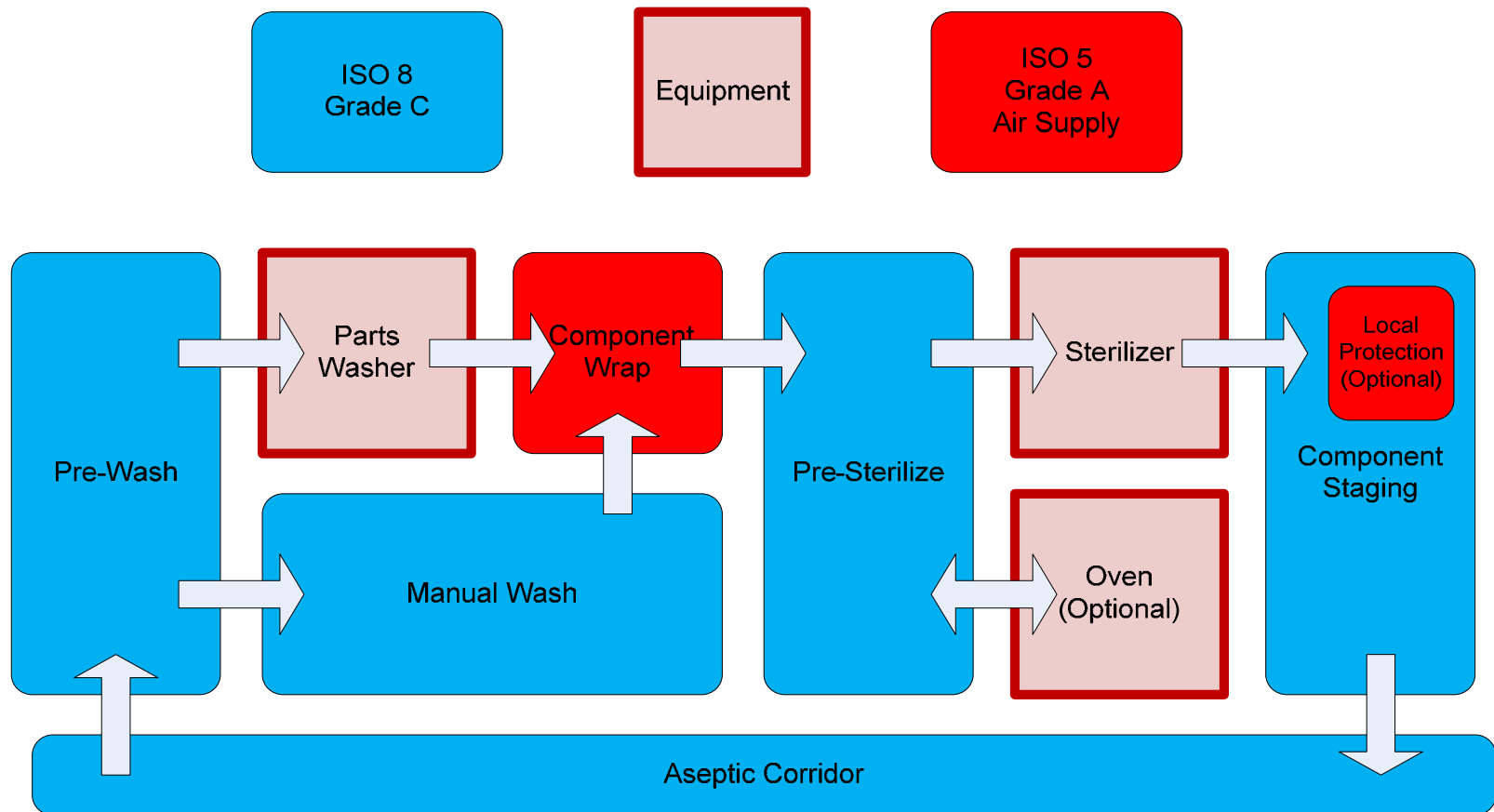
Syringe Filling Room - 1



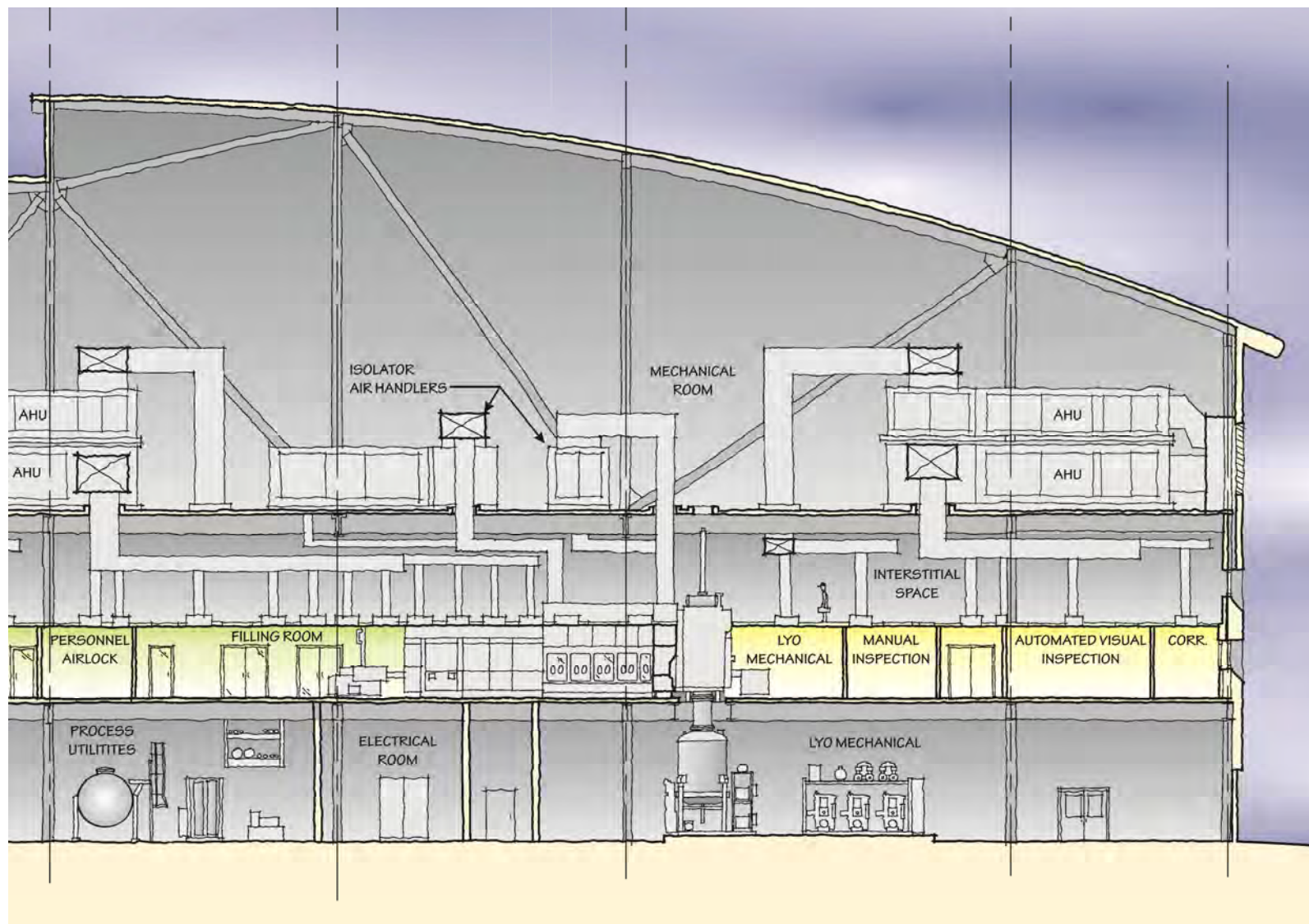
Formulation Suite



Component Prep Suite



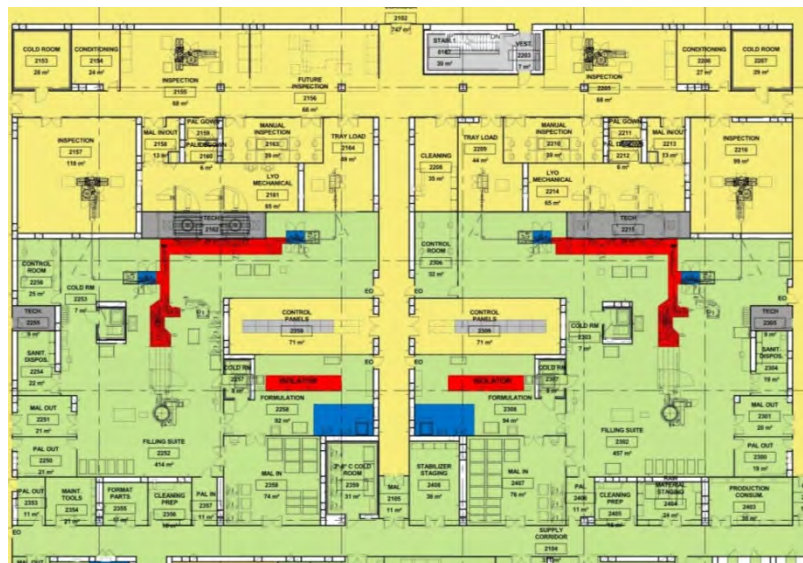
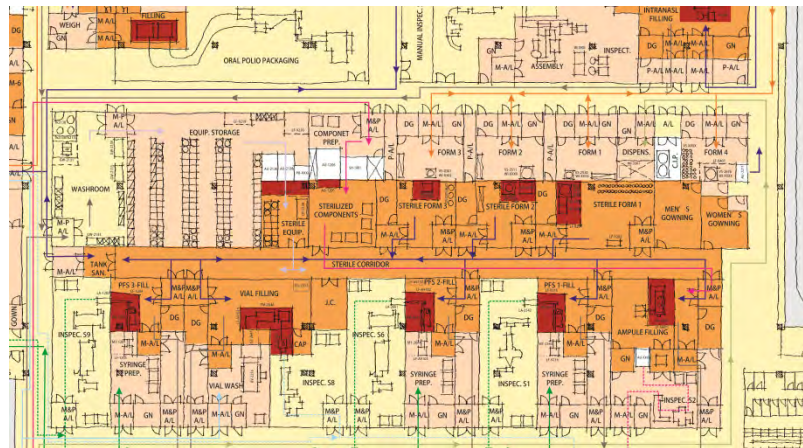
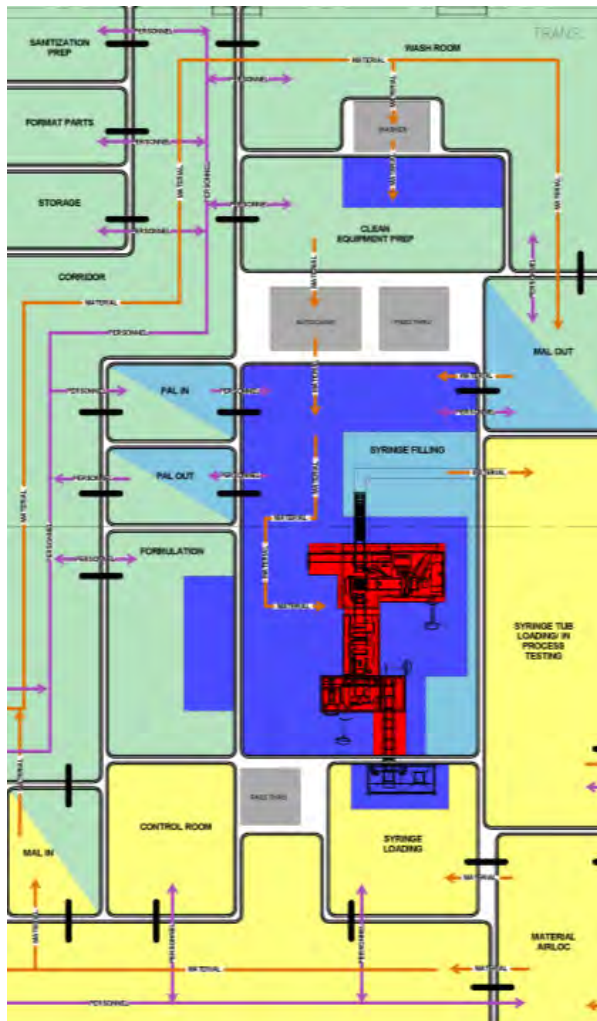
Ideal Building Section



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Facility Layout Options

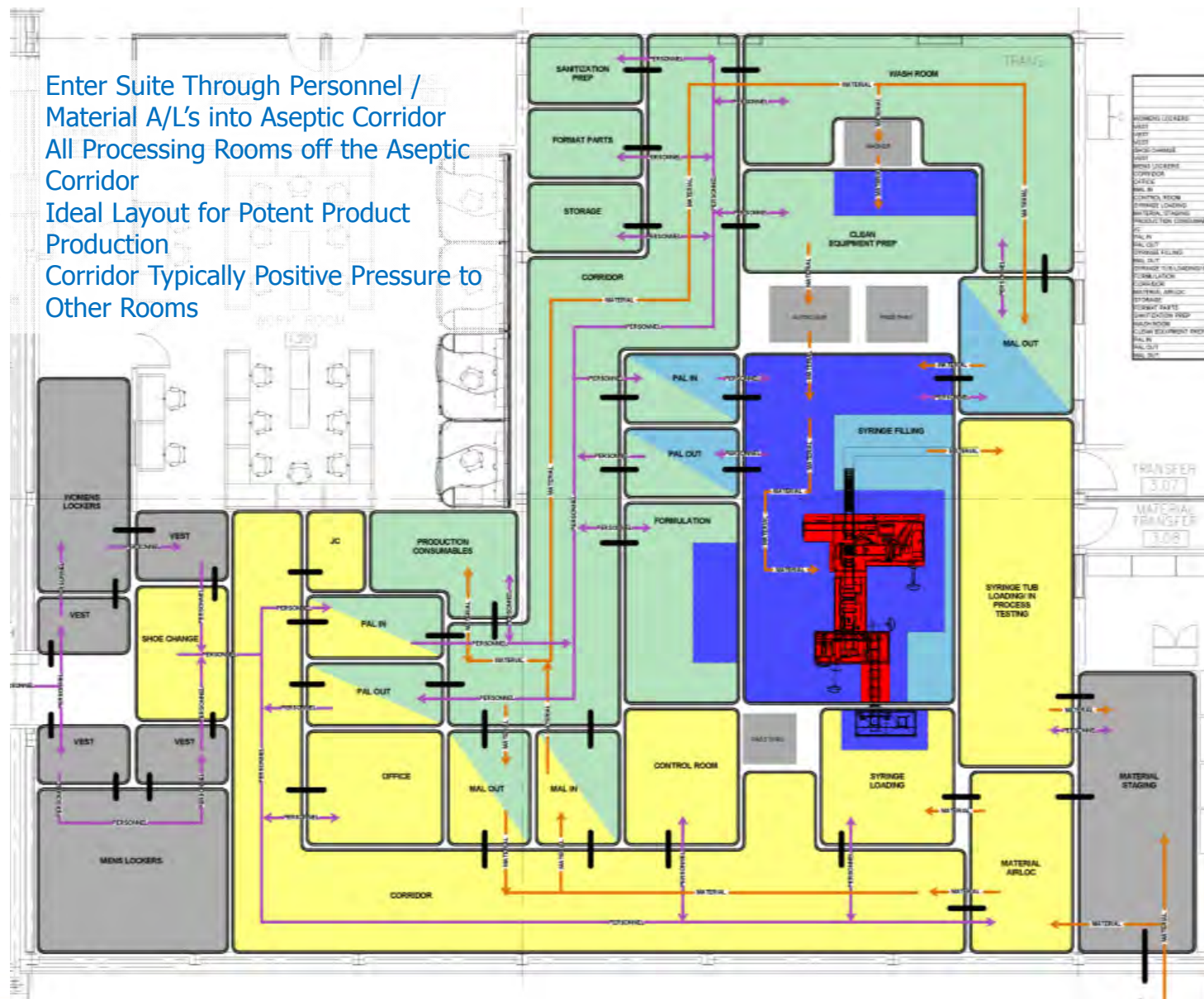


The floor plan illustrates a complex pharmaceutical manufacturing facility with a clear separation of material flow paths. The top section contains equipment storage, washrooms, and gowning areas. The middle section is dedicated to sterile processing, including sterilized components, sterile equipment, and a central sterile corridor. The bottom section focuses on product filling and inspection, with areas for PFS (Pre-Fill System) filling, vial filling, syringe preparation, and vial washing. Material flow is meticulously tracked using color-coded arrows: blue for general material flow, green for sterile material flow, and red for waste flow. The plan also includes a material in/out buffer, intermediate cold storage, and a breakroom.

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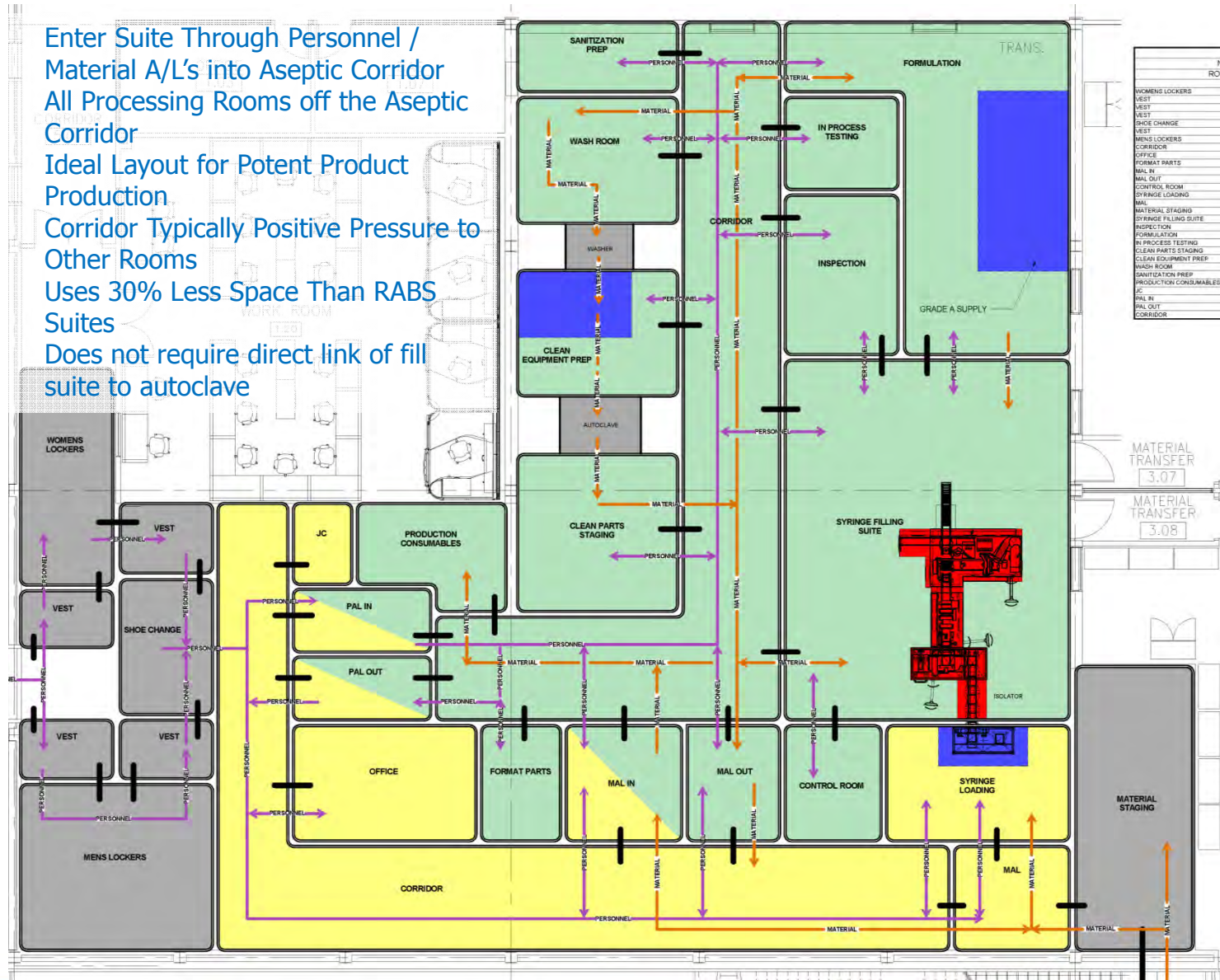
Single Line - Aseptic Corridor - RABS

- Enter Suite Through Personnel / Material A/L's into Aseptic Corridor
- All Processing Rooms off the Aseptic Corridor
- Ideal Layout for Potent Product Production
- Corridor Typically Positive Pressure to Other Rooms



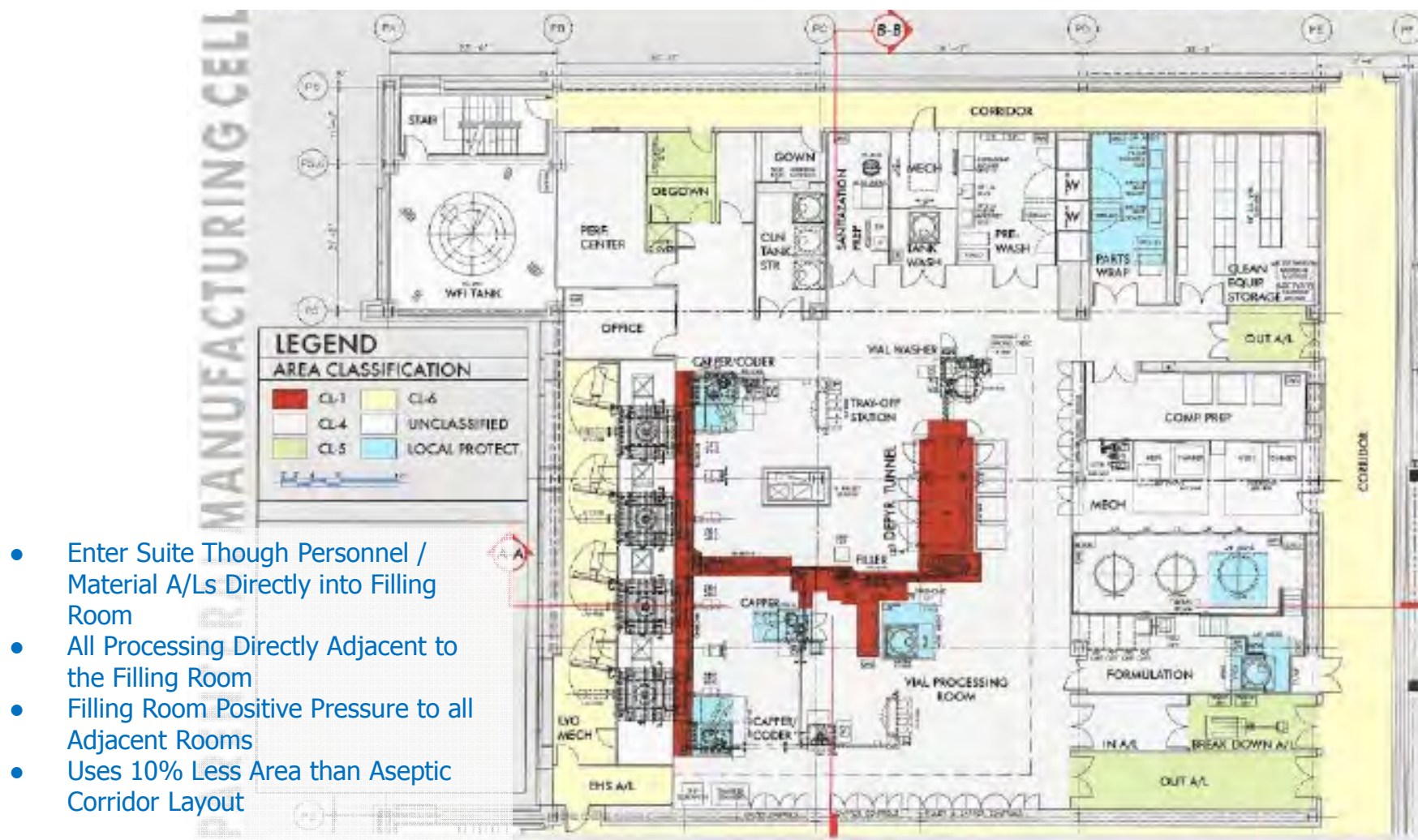
Single Line - Aseptic Corridor - Isolator

- Enter Suite Through Personnel / Material A/L's into Aseptic Corridor
- All Processing Rooms off the Aseptic Corridor
- Ideal Layout for Potent Product Production
- Corridor Typically Positive Pressure to Other Rooms
- Uses 30% Less Space Than RABS Suites
- Does not require direct link of fill suite to autoclave



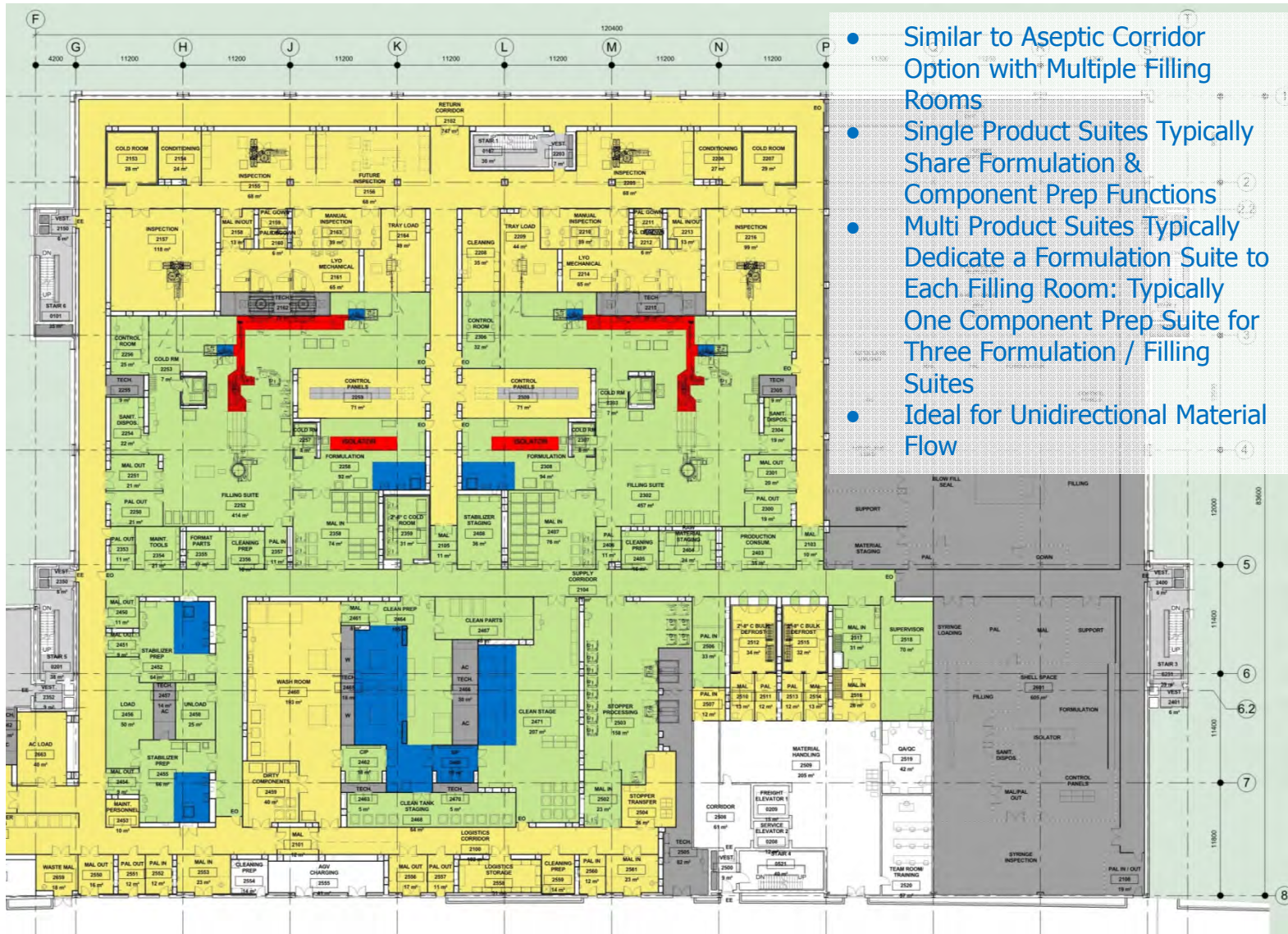
- Enter Suite Though Personnel / Material A/Ls Directly into Filling Room
- All Processing Directly Adjacent to the Filling Room
- Filling Room Positive Pressure to all Adjacent Rooms
- Uses 10% Less Area than Aseptic Corridor Layout

Single Line – Ball Room - Isolator

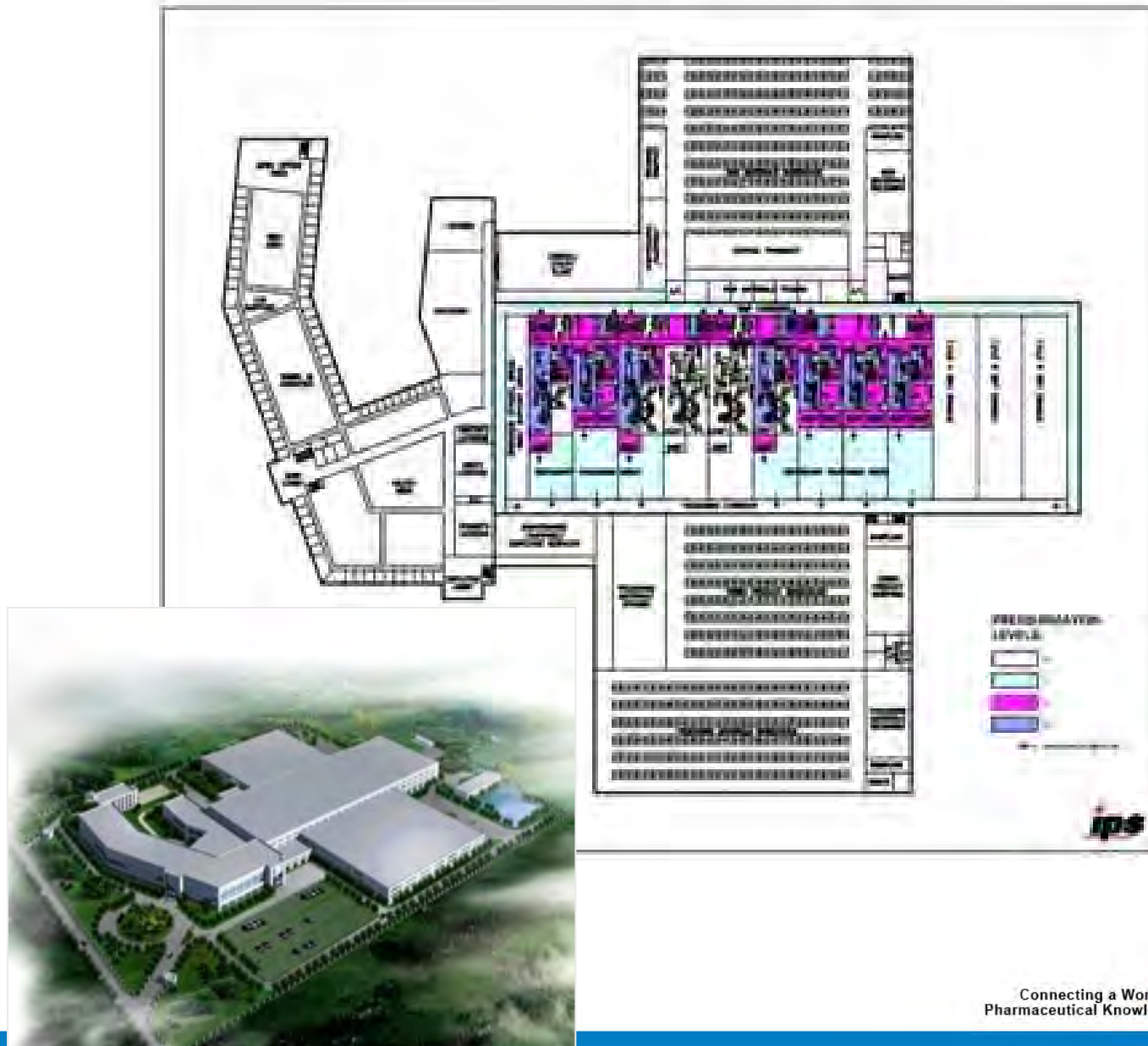


- Enter Suite Though Personnel / Material A/Ls Directly into Filling Room
- All Processing Directly Adjacent to the Filling Room
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- Uses 10% Less Area than Aseptic Corridor Layout

Parallel Delivery – Isolator



Parallel Delivery – Isolator



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Multi-Delivery – Isolator

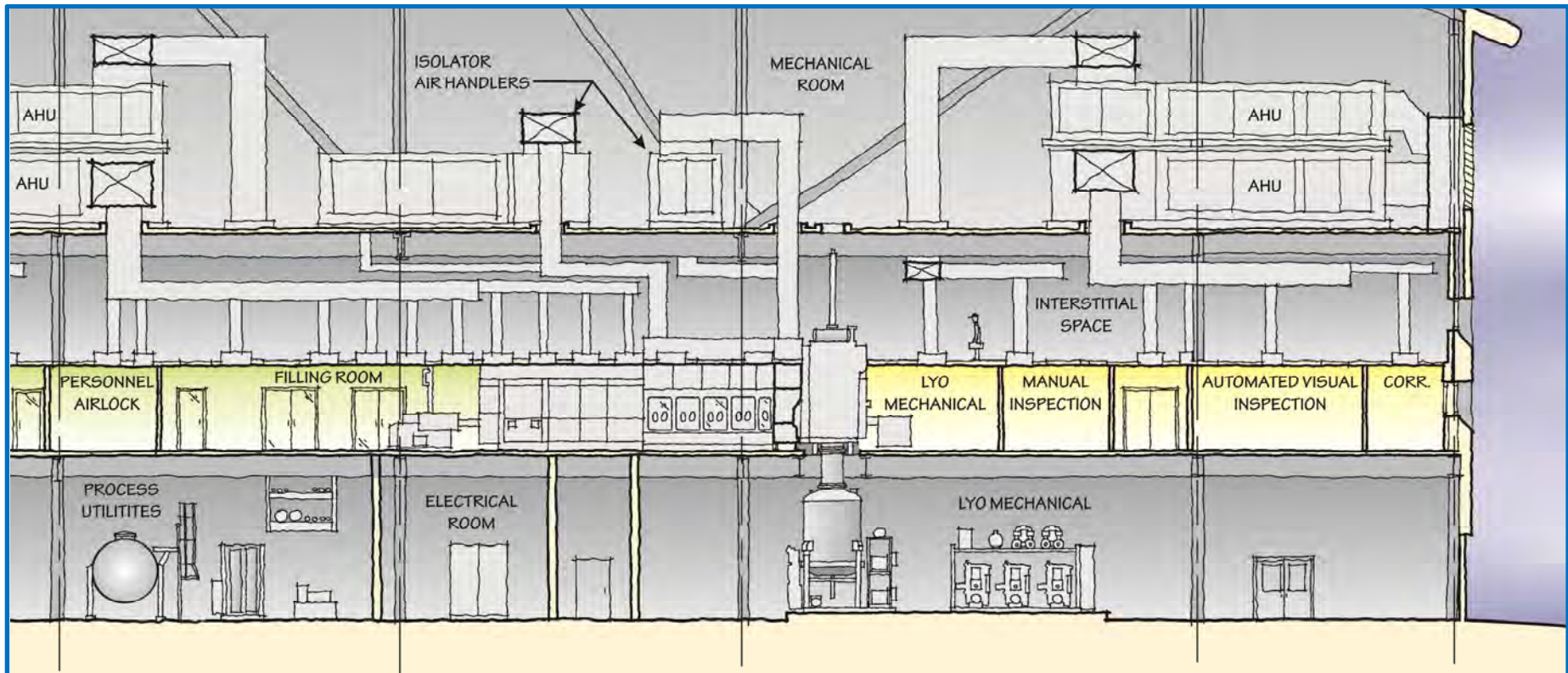


- Variation of Parallel Filling Line Option Using Several Different Delivery Systems
- Leverage Grade C/ISO 8+ Suite for:
 - Isolated Liquid / Lyo Vial Lines
 - Isolated Nested Syringe Lines
 - Isolated Bulk Syringe Lines
 - Terminally Sterilized Vial or Syringe Lines
 - BFS Lines

Aseptic Facility Design Summary

- **Regulatory Perspective:** *'The Advantage of Closed Systems is Substantial.'*
- **Barrier Technology:** The industry is moving towards barrier technology and regulatory agencies will be expecting to see in in new facilities.
- **Historical Perspective:** Today's isolators are easier to operate and have proven automated decontamination cycles.
- **Choosing a Barrier Technology:**
 - The design of the facility is driven by the barrier technology
 - Isolators provide the lowest risk with the greatest separation between people and products.
 - Aseptic Suites for Isolator Based Facilities are 30% Smaller then traditional or RABS based faciltites and operational costs are lower.
- **Aseptic Facility Design:** Modern faciltites should encourage cGMPs by optimizing flows, providing product segregation and operator safety

Discussion - Questions?



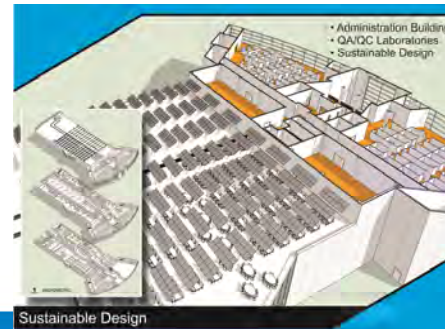
THANK YOU



Fill/Finish Facility



Master Plan - Exploded Axonometric



Sustainable Design

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