PhEn-602
Pharmaceutical Facility Design

Notes # 8

J. Manfredi

Architecture & Layout Considerations

Important to understand the manufacturing processes and conduct the facility programming.

Facility ***layout*** must be an integrated design that satisfies the following:

- **Process requirements**
- **Personnel flows**
- **Material flows (product, component and raw material movements)**
- **Equipment layout requirements**
- **Operational access requirements**
- **Maintenance access requirements**

Architecture & Layout Considerations

The layout of the sterile manufacturing facility must be developed around the needs of the facility.

The needs of the facility are defined during the facility programming stage.

Architecture & Layout Considerations

During the programming phase, the firm must define their true needs…they must separate the "must have" objectives from their "wants" objectives.

This is often a very time consuming effort, since each department needs to re-think what is truly mandatory for their operation versus those items that are desirable, but not essential to successful operations.

Formal decision analysis may need to be performed.

Architecture & Layout Considerations

Architectural design must consider proper room finishes, environmental and safety considerations, and must ensure that design is compliant with building codes and fire regulations.

Structural framework and building exterior finishes must take into account the interior room environment (i.e.: Minimize the use of columns and expansion joints within the cleaner areas of a manufacturing facility where possible).

Architecture & Layout Considerations

The architect must build the facility around the equipment and systems required for the process…..

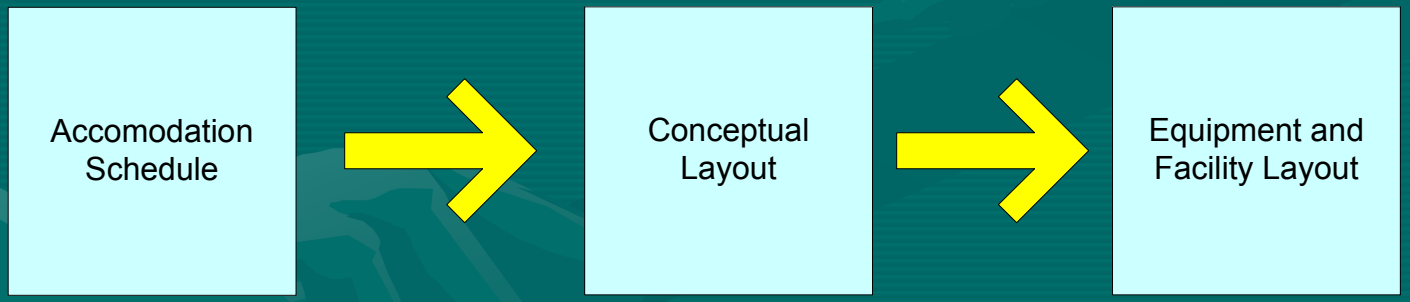
Architect must understand the flow of personnel and materials!

Architecture & Layout Considerations

- Area classification and hazards must be reviewed
- Are potent compounds involved/handled?
- Are flammable liquids used in formulations?
  - Explosion proof design may be required.
    - Explosion proof panels require special construction methods and impact layout issues.
- Are chemically resistant finishes needed?
- Service penetrations and routing of utilities must consider interior layout
  - Minimize piping mains above clean areas
    - Route to less clean areas to the extent possible
- Location of process viewing panels (visibility) is important

Architecture & Layout Considerations

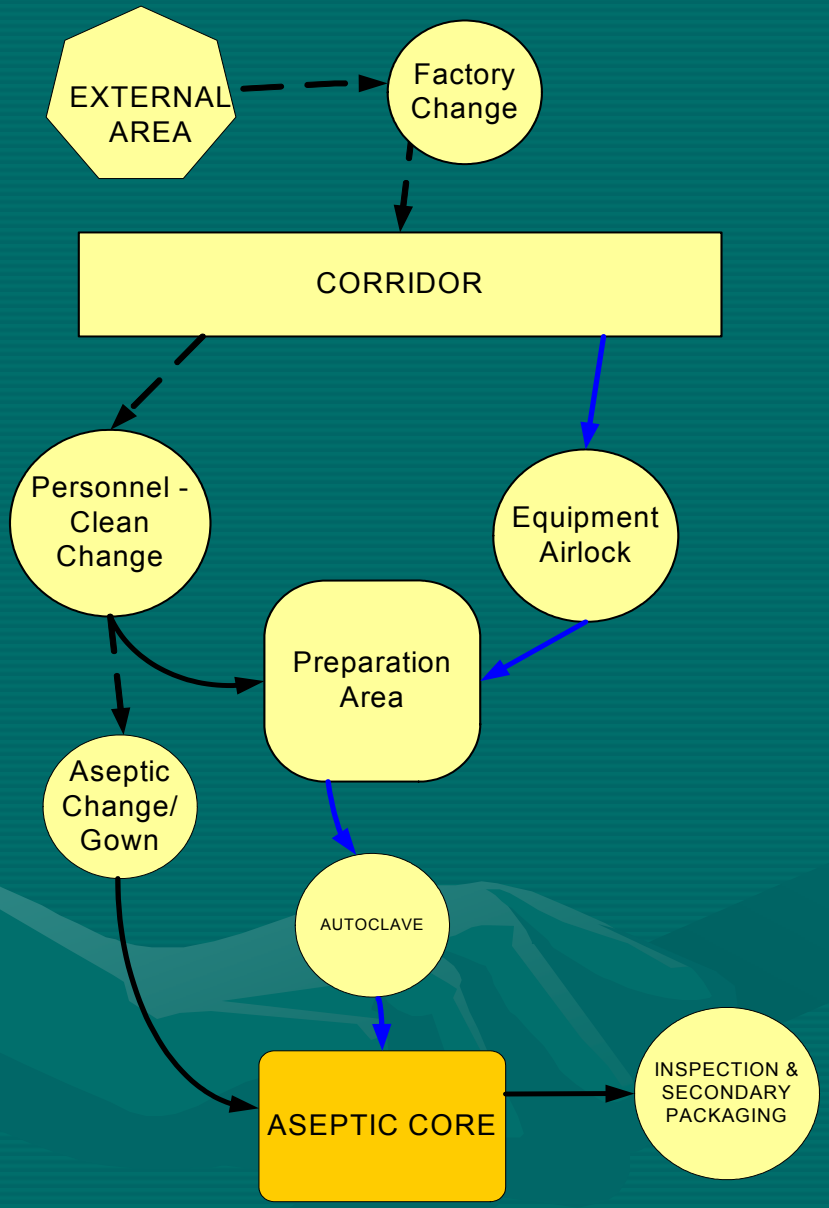
- The designer must first understand the product and process requirements.
- Accommodation Schedule is the first step



Architecture & Layout Considerations

Accommodation Schedule:

- Defines all areas that can influence unit operations required for manufacturing as well as the relationships and flows between them
- Materials and personnel are primary focus
- Can be developed once the process is known
  - All process flow diagrams should be complete
- Also referred to as logic diagrams, or bubble diagrams



Accommodation Schedule

Architecture & Layout Considerations

Conceptual Layout

- Derived from Accommodation Schedule and equipment sizing needs
- Building blocks of equipment lines are developed
- Blocks of rooms are assembled based on necessary adjacencies and process requirement

Architecture & Layout Considerations

Equipment Layout

- Scaled drawing derived from conceptual layout
- Defines precise room sizes, structural grids
- Access routes
- Building and fire codes, means of egress are established in this phase. Building blocks of equipment lines are developed
- Blocks of rooms are assembled based on necessary adjacencies and process requirements
- Part of detail design phase of project life cycle

Architecture & Layout Considerations

After Equipment Layout Drawings are prepared, establish Material and Personnel Flows

- Superimposed on Equipment Layout Drawings
  - Typically superimposed with directional arrows
- Primary purpose is to illustrate how to eliminate or minimize the potential for contamination of the clean room product and personnel.
- Layout should prevent cross contamination
- One-way flow always preferred
- Provide separate entry and exit ways of possible, particularly in changing areas.
- Separate gowning and de-gowning areas always preferred

Architecture & Layout Considerations

Material and Personnel Flows

- One-way flow is always preferred, as long as all other needs can be maintained
  - Often not possible when retrofitting an existing facility
- Avoid simultaneous two-way flow through a common area
  - Door interlocks and alarms used for prevention
- Gowning areas separated entry from exit
- Layout should prevent entry of personnel into clean/critical areas without first going through gowning room
- Airlocks should be used between areas of different classifications (e.g. between controlled and critical areas).
  - Airlocks should have door interlocks to prevent simultaneous two-way flow

Architecture & Layout Considerations

- Personnel flows considered:
  - Manufacturing personnel
  - Maintenance personnel
  - Quality control personnel

Architecture & Layout Considerations

- Material flows considered:
  - **Raw materials**
  - **Finished goods**
  - **Waste**
  - **Product (In-process, Intermediate & Final)**
  - **Equipment**
    - **Clean and dirty components**
    - **Portable equipment**
    - **Product containers**

Architecture & Layout Considerations

- Provide sufficient space for operations
- Provide sufficient space for movement, equipment access and egress for life safety code requirements
- Rooms must be sized only after you fully understand what goes into the room, and the process that takes place between the four walls
- Can't overlook need for extra space for portable items brought into the room, such as carts.
- Mechanical and electrical equipment panels also need to be taken into account.

Architecture & Layout Considerations

Cost considerations in layout design:

- Layout has significant impact on the amount of materials and therefore facility cost
- Minimize perimeter vs. internal area, to reduce costs of external load bearing walls and insulation.
- Simple plan shapes are most economical
  - Square maximizes internal area, minimizes perimeter
- Minimize building height
- Minimize number and size of clean rooms, particularly Class 100 rooms
- Minimize size of clean corridors and staging areas

Architecture & Layout Considerations

Minimize height of building to extent possible.

Height increases cost due to:

- Increase in amount of perimeter wall for a given total floor area
- Increased load on the structure
  - Heavier load on columns and footings
- Additional hoisting of materials and extra time taken by operators to reach the higher floors

Architecture & Layout Considerations

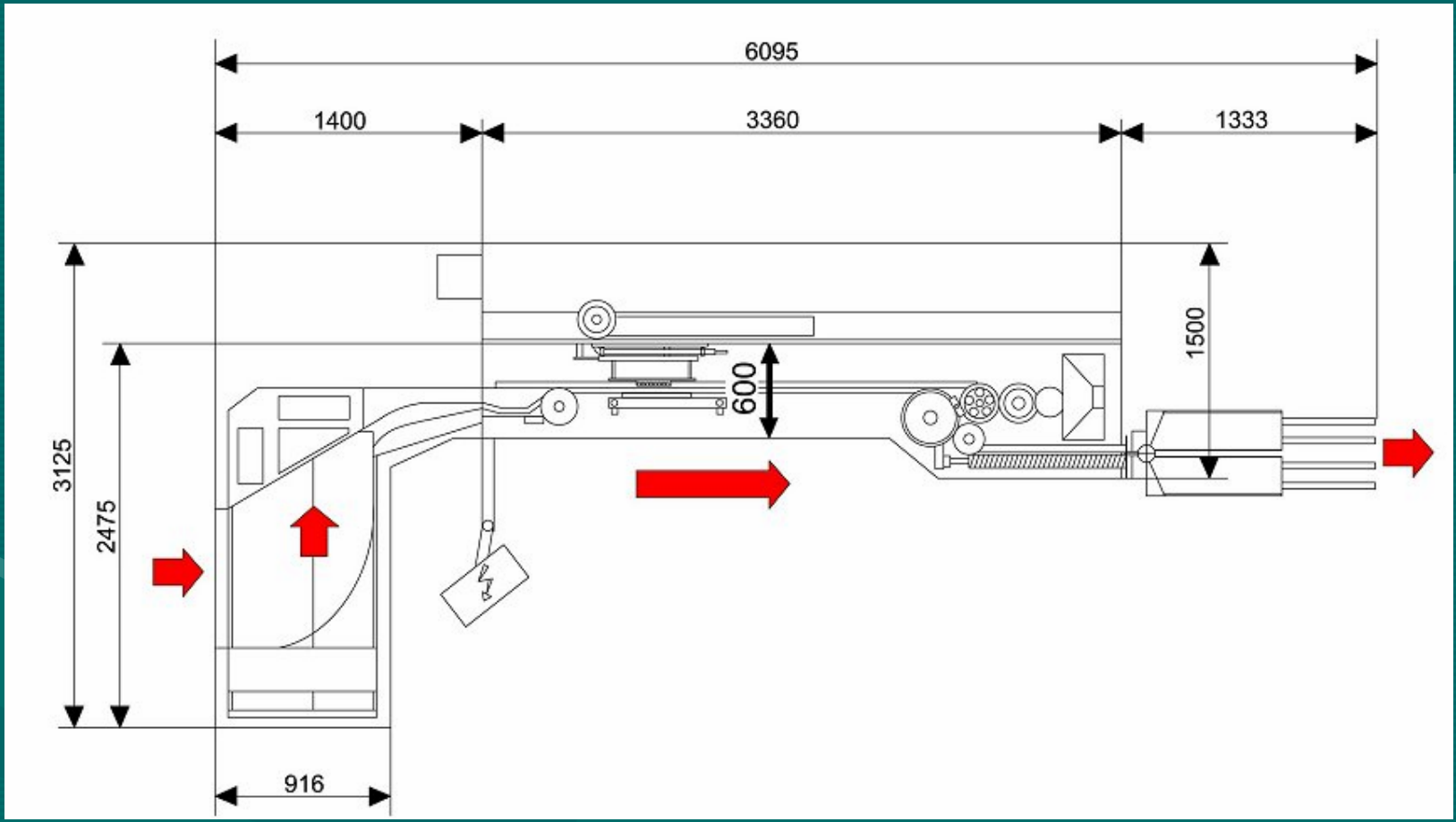
- Thermal currents
- Unidirectional airflow shading

GMP's 21 CFR Part 211

– Subpart C-Buildings and Facilities

- **§ 211.42 Design and construction features.**
- (a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of **suitable size**, construction and location to facilitate cleaning, maintenance, and proper operations.
- (b) Any such building shall have **adequate space** for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination.
- The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be **designed to prevent contamination**.
- (c) Operations shall be performed within specifically defined **areas of adequate size**.

Example Equipment Layout



Architecture & Layout Considerations

- Room criteria sheets help to define the requirements upfront (also referred to as Lab Cards)

Room Name:		Main Compounding Room	
General Area:		Compounding	
Room no.		128	
Structural			
			Hoist
			Monorail
			Floor pits (scales)
Operational Issues:			Three fixed tanks, 100 L, 500 L, 1,000 L
			wash down
			Special material handling
			Purified water Drop (3 use points)
Miscellaneous:			Wall bumpers
			Roof hatches
			Armor plate on doors
			Shelving
			Storage cabinet

Architecture & Layout Considerations

Gowning rooms play a critical role in the facility layout.

Cleanroom clothing:

- Designed to limit the rate of particle generation from the person
- Designed to limit the rate of particle generation from the clean room garment.
- In cleanrooms where contamination is not as important (e.g. pharmaceutical areas and Class 100,000 areas), smock, cap and shoe covers may be appropriate.

Architecture & Layout Considerations

Changing rooms:

Two grades (levels) of changing rooms

- Low (standard)
  - From normal clothing (street clothes) to factory (clean) clothing
- High (standard)
  - From clean clothing to full coverage suit

Architecture & Layout Considerations

Cleanroom clothing requirements are found in:

- IEST Recommended Practice RP-CC-003.2
- EU Guidelines

Architecture & Layout Considerations

Cleanroom clothing:

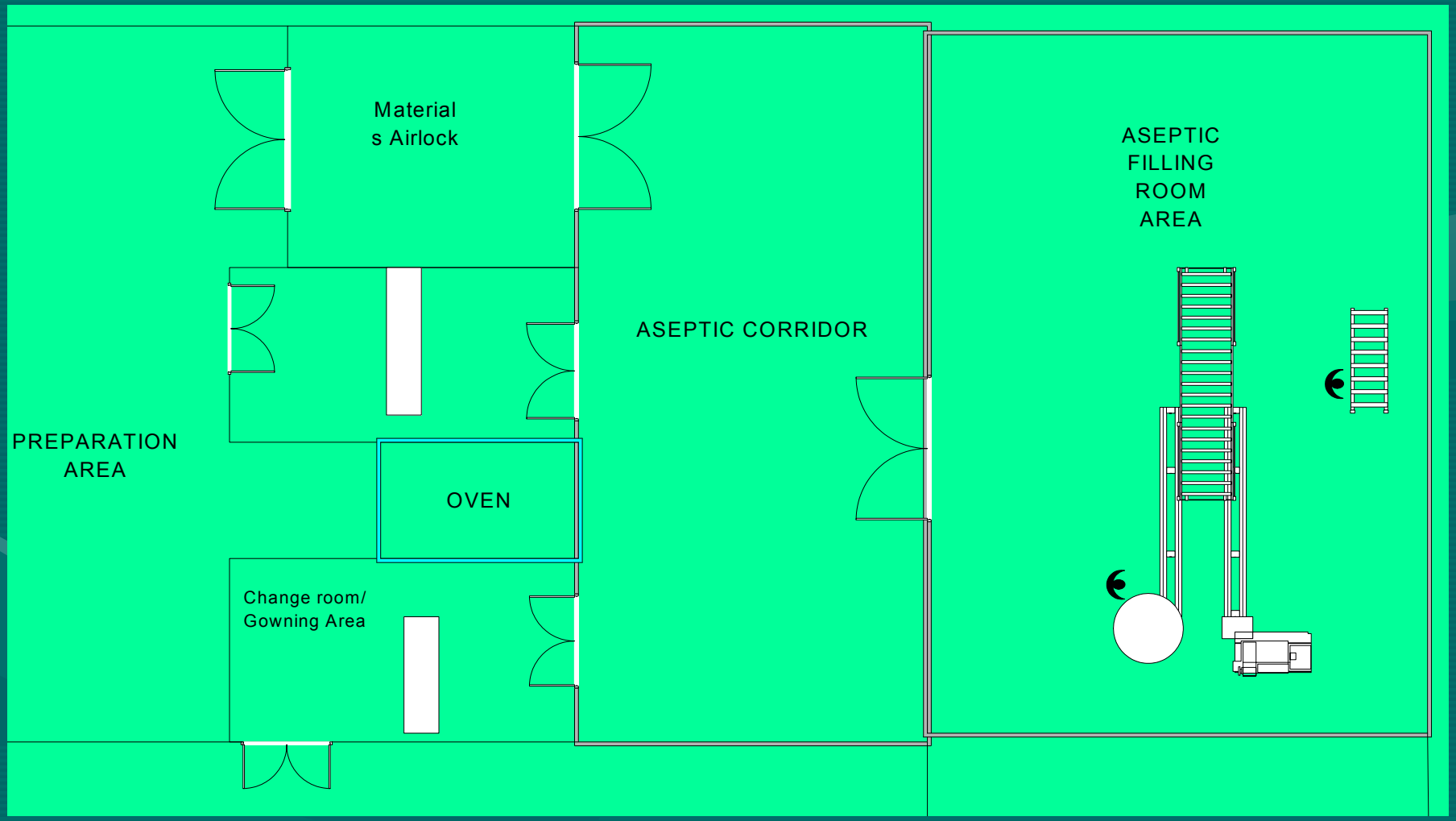
- In cleanrooms where contamination is critical, (e.g. Class 10,000 and Class 100 areas), a full coverage coverall, hood, boots, mask, gloves and goggles are worn.

Architecture & Layout Considerations

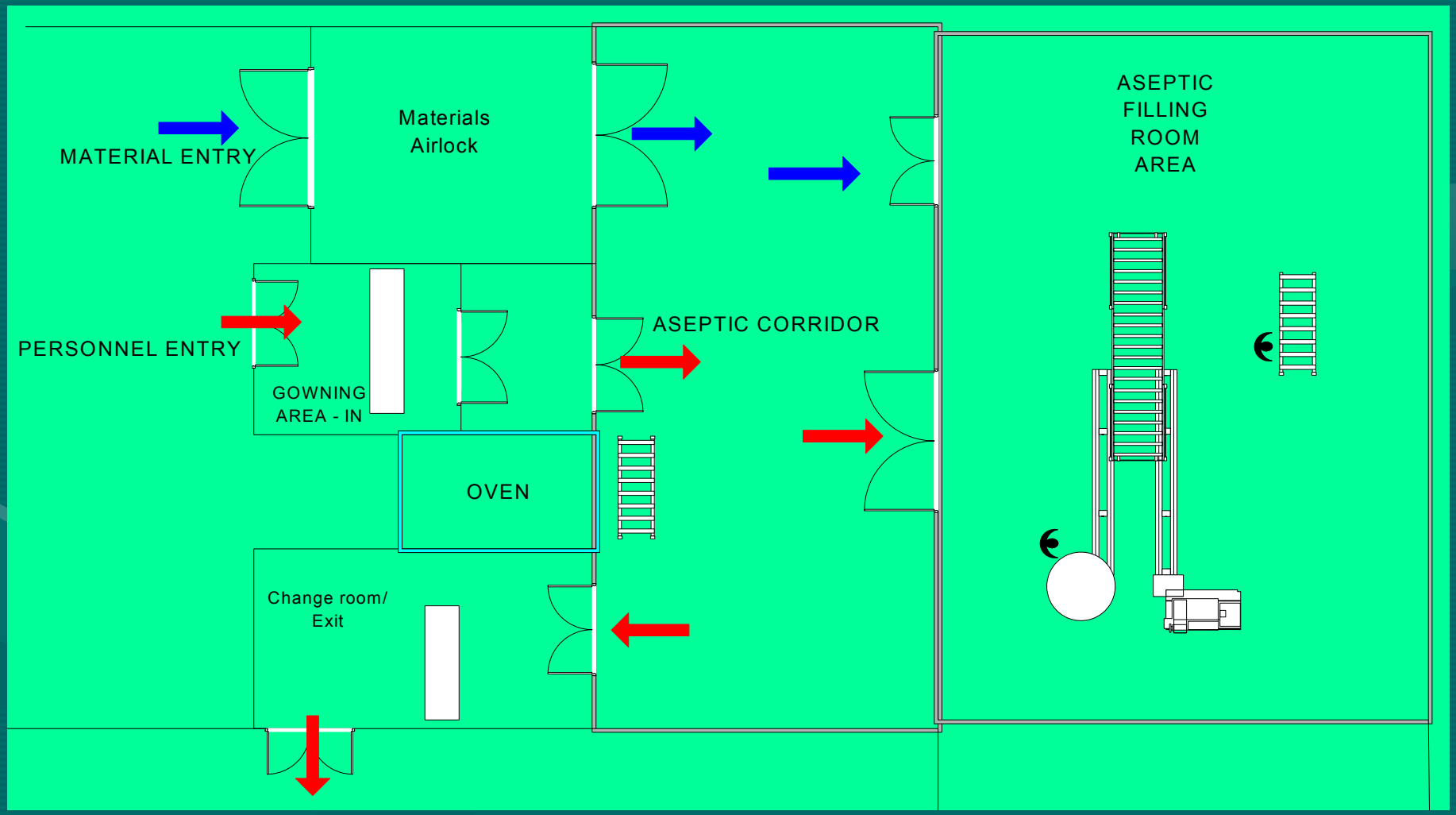
Gray zones: Service space or maintenance space typically adjacent to the production room

- Contains the majority of piping, valves, electrical conduit and other utilities that support the manufacturing area.
- Maintenance personnel have separate access to these areas, allowing less stringent gowning requirements, and allows for maintenance without shutting down or disrupting the manufacturing operation

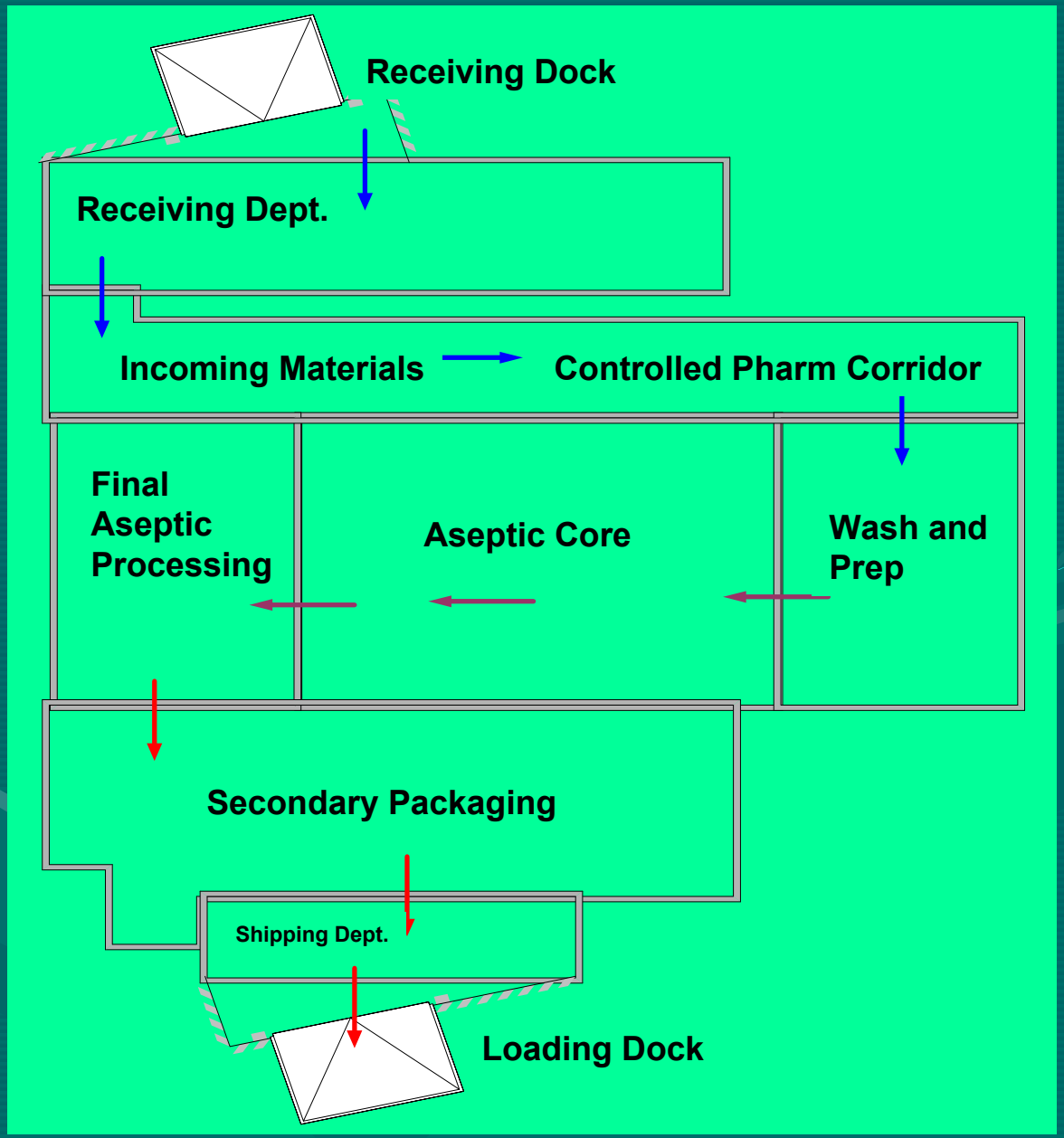
Example Layout



Material & Personnel Flow Example



Desirable Layout



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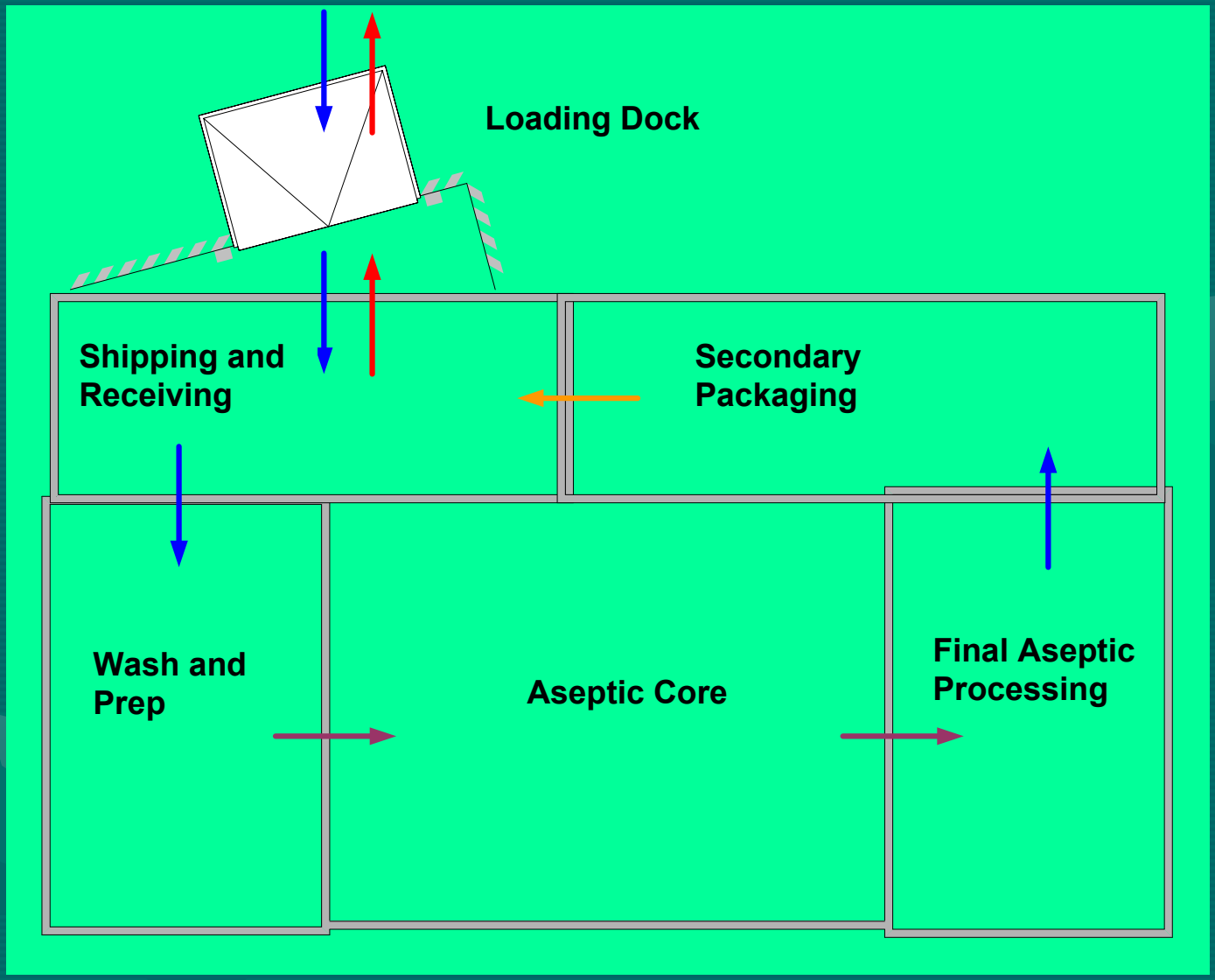
Less Desirable Layout



Materials of Construction & Surface Finishes

Materials of Construction & Surface Finishes

- **§ 211.42 Design and construction features.**
- There shall be separate or defined areas for the firm's operations to prevent contamination or mixups as follows:
- (10) Aseptic processing, which includes as appropriate:
- (I) **Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;**

Materials of Construction & Surface Finishes

- There is no such thing as FDA endorsed materials
- Surface finishes should be smooth, non-shedding, non-porous, and resistant to sustaining microbial growth
- Finishes must withstand repeated cleaning and sanitization* without evidence of rust, or peeling paint.

  *Cleaning and sanitization agents include detergents and disinfectants, as well as hot WFI.
- Stainless steel often used throughout the facility because of its appearance, durability, smoothness, and resistance to rust, peeling and shedding

Materials of Construction & Surface Finishes

- Ledges, joints, and corners difficult to reach should be minimized
- Door hardware should be minimized
  - Use proximity sensors wherever possible
- A cleanroom should be built airtight, where possible
- Internal surfaces smooth and suitable for cleaning
- Surfaces must be resistant to impact
- Joints should be free of openings that could harbor dirt or microbes
- Crack and crevice-free construction

Materials of Construction & Surface Finishes

- Concealed, sealed sprinklers should be used to avoid communication between cleanroom and interstitial space
- Electrical outlets should be covered/sealed suitable for washdown service
- Predetermined routes for removing/installing tanks and other stationary equipment
  - Removable wall panels often used to avoid tear-out later.
- Bumper guards on doors and corridors that are subjected to heavy equipment travel

Materials of Construction & Surface Finishes

- Platforms typically stainless steel, including decking, stairs and support structure
- Stainless steel screens on HEPA filters
- Stainless steel benches for gowning areas
- Recessed fire extinguishers with stainless steel frame
- All access panels stainless steel

Materials of Construction & Surface Finishes

Materials of Construction & Surface Finishes

Flooring: Consider aesthetics, durability and cleanability

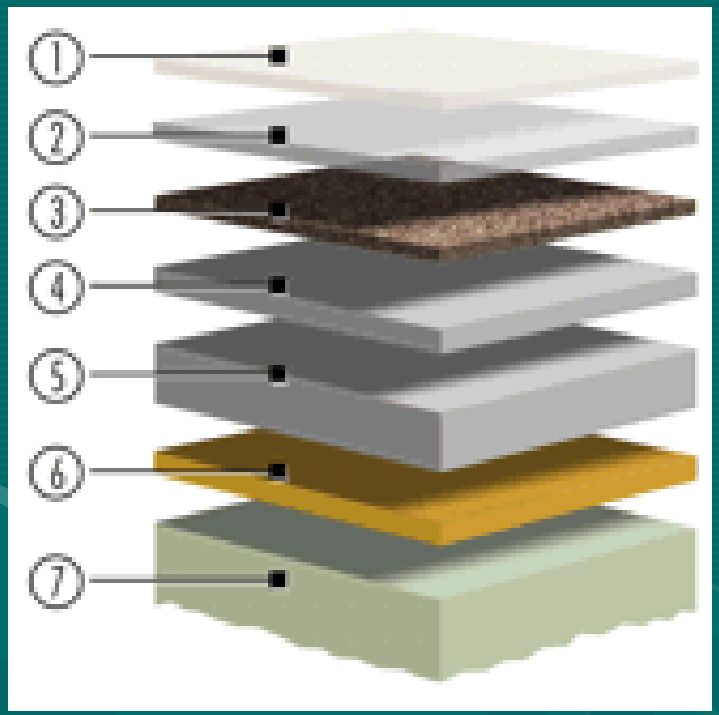
- Epoxy terrazzo:
  - hard, durable long-lasting surface with excellent chemical resistance
  - Very expensive to install
- Epoxy Resin Systems: (e.g. Stonhard)
  - Very popular in the Pharmaceutical industry
  - Easier to install than Terrazzo
  - Moderate durability and chemical resistance
  - Moderate price
- Welded Vinyl/PVC Sheet (e.g. Mipolam)
  - Durability an issue in high-traffic areas
  - Often used with identical wall system for matching

Materials of Construction & Surface Finishes

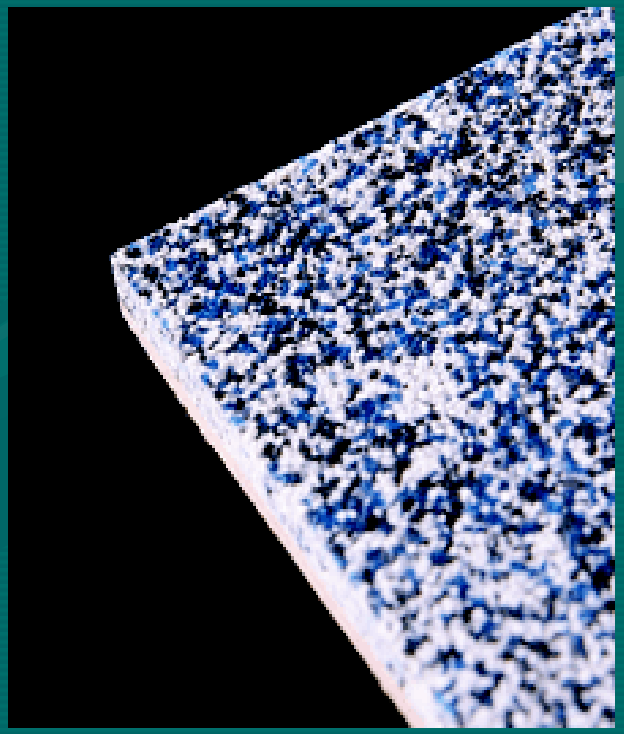
Mipolam

Materials of Construction & Surface Finishes

Typical seamless epoxy resin flooring system



1.Polyurethane Coating (Gloss or Matte)
2.Epoxy Clear Coat
3.Broadcast
4.Epoxy Coat
5.Heavy Duty Mortar
6.CornerCrete Slurry Primer
7.Substrate

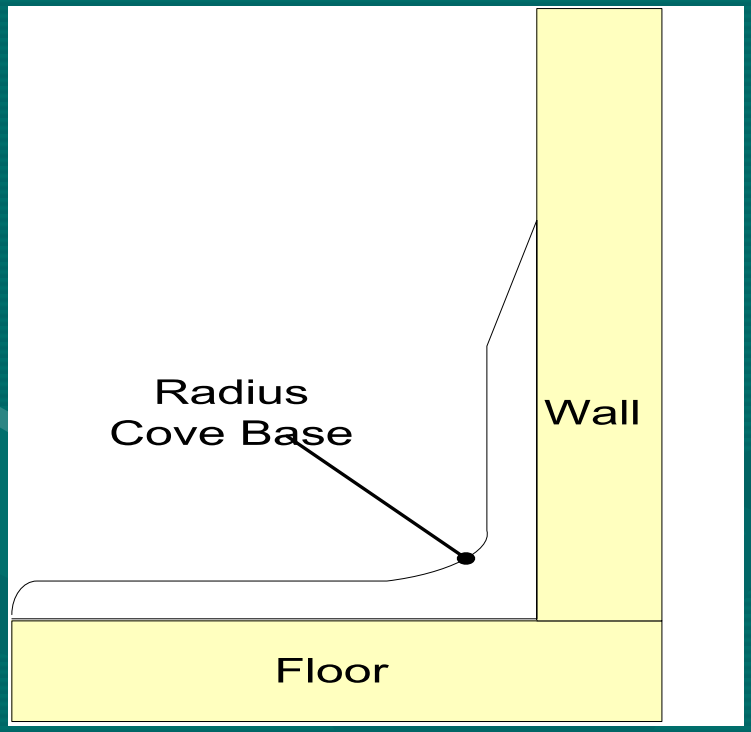


Flooring

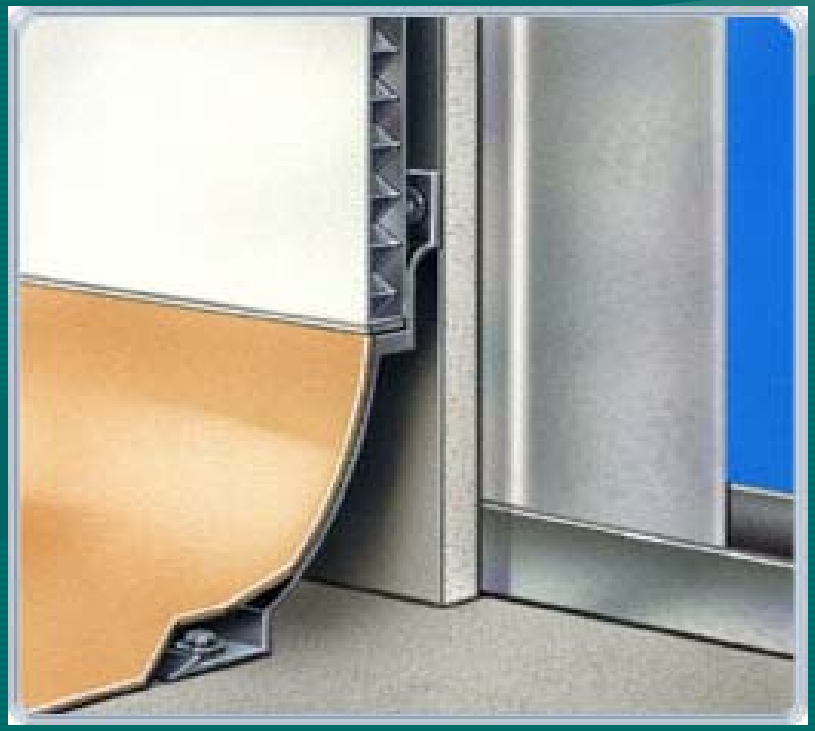
- Epoxy terrazzo:
  - hard, durable long-lasting surface with excellent chemical resistance
  - Very expensive to install

Materials of Construction & Surface Finishes

Radius cove base typically used



Radius cove base in modular construction



Materials of Construction & Surface Finishes

Flooring/drains

- Drains should be avoided in Class 100 through Class 10,000 rooms.
- Acceptable in Class 100,000 rooms

Materials of Construction & Surface Finishes

Ceiling Systems

- Same issues are important: aesthetics, durability and cleanability
- Gypsum Wall-board (GWB) with finish coat of epoxy paint
  - Pro's:
    - Flexible, easy to use
    - Most common in the industry
  - Con's:
    - Restricts future above-ceiling access
    - Requires careful coordination with other trades during construction. (e.g. piping penetrations, HVAC diffusers, light fixtures, filter housings).

Materials of Construction & Surface Finishes

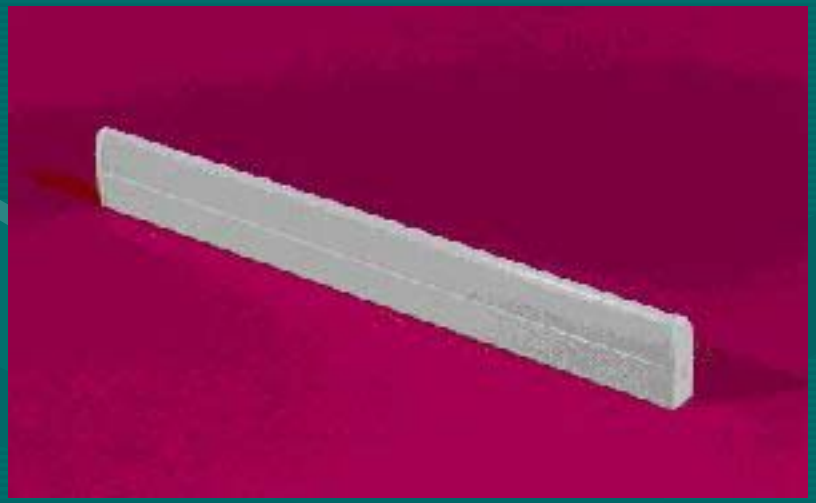
Ceiling Systems

- Lay-in grid ceilings (http://www.cleanroomeng.com/products_ceiling.cfm)
  - Use gasketed clean-room tiles
  - Seams and joints still a potential breeding ground for bacteria

Materials of Construction & Surface Finishes

Light fixtures

- Lay-in grid ceilings
  - sealed units with stainless trim
- Teardrop



Materials of Construction & Surface Finishes

For Class 100 through Class 10,000 (Grade A and Grade B areas), radius coves are often used in the ceiling to wall junction as well

Radius cove where ceiling meets wall. (modular construction shown).

Materials of Construction & Surface Finishes

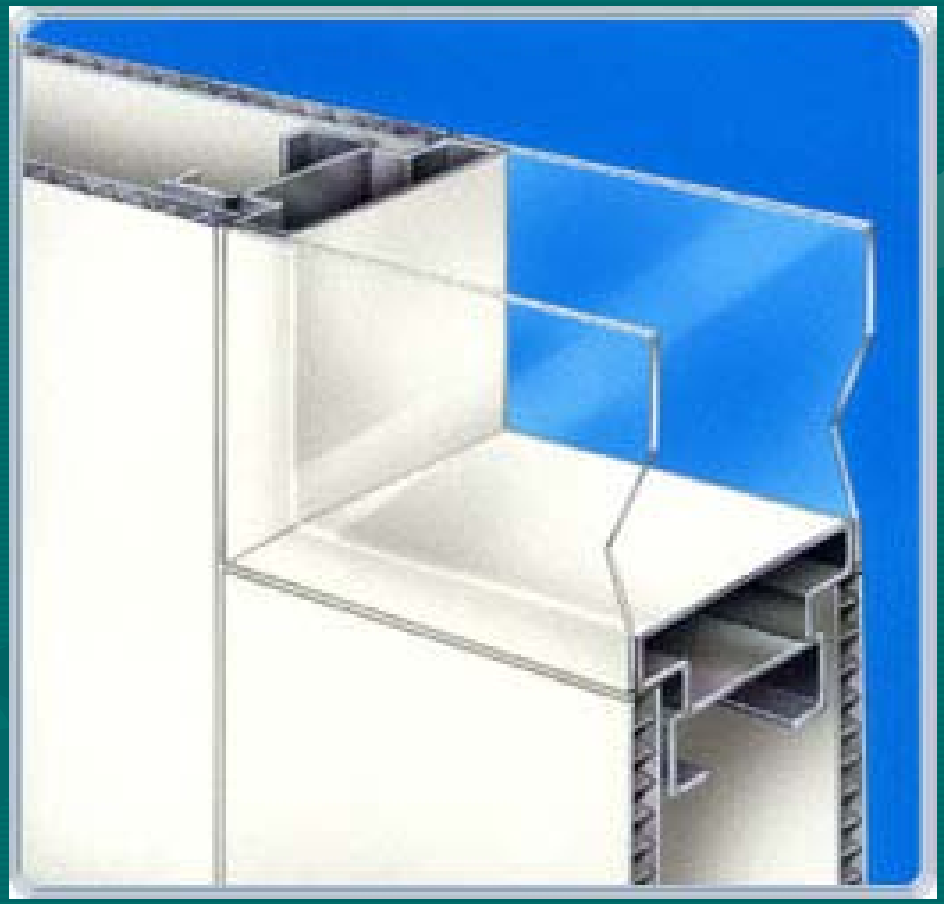
Wall systems

- Consider aesthetics, durability and cleanability
- Gypsum Wall-board (GWB) with epoxy paint finish
- Concrete Block/concrete block with plaster
- Epoxy Resin walls
- Welded sheet PVC (e.g. Mipolam)
  - Typically used in higher class areas (e.g. Class 100)

Materials of Construction & Surface Finishes

Wall systems
(Vision Panels)

- Flush with the wall to eliminate ledges
- Often Stainless frame, double pane
- Free of gaps along the perimeter



Materials of Construction & Surface Finishes

Cleanroom Doors

Full glass or half glass architectural aluminum doors are available with a variety of hardware options, including pivot hinges, surface mounted closers, concealed closers, panic hardware, and locksets.

Materials of Construction & Surface Finishes

Steel Doors

Glazed or flush steel doors integrate into the aluminum door frames utilizing butt hinges at the jamb connection.

Materials of Construction & Surface Finishes

Electric Sliding

Sliding doors easily integrate into wall systems and are available in any size with a variety of hardware available including push button entries and motion sensors.

Materials of Construction & Surface Finishes

High-Speed Roll-Up Doors

Roll Up Doors offer advantages over swinging doors, sliding doors, and strip curtains. Doors can be created up to 18' x 18'. Suitable for Class 100,000 to Class 10,000 applications. The door opens and closes quickly reducing the time the cleanroom interior is exposed.

Materials of Construction & Surface Finishes

Glazing

Windows and doors can be glazed with a variety of options as specified by the project requirements. One can choose from tempered glass, tinted glass, Lexan, acrylic, static dissipative, film-covered glass or solid panels

Materials of Construction & Surface Finishes

AIR SHOWERS

Chambers located between the clean room and an outside environment that remove particulate contamination from clean room garments as personnel pass through. The chambers may include HEPA filters, interlocking doors, a re-circulating air system, and air nozzles in various patterns through which filtered air is blown onto the personnel in the shower. The high-velocity air is moved over the worker, removing particulate contamination from the worker's garments.

Materials of Construction & Surface Finishes

Modular Cleanroom Facilities

Self-contained facilities built off-site under controlled conditions, then delivered and integrated into the final point of use location with the minimal amount of reassembly.

- Very popular alternative.

Three ISPE Facility of the Year Awards were given to firms that utilized the modular concept.

- Novo-Nordisk, Denmark
- Baxter Biopharma Solutions, Bloomington, Indiana
- GSK

Materials of Construction & Surface Finishes

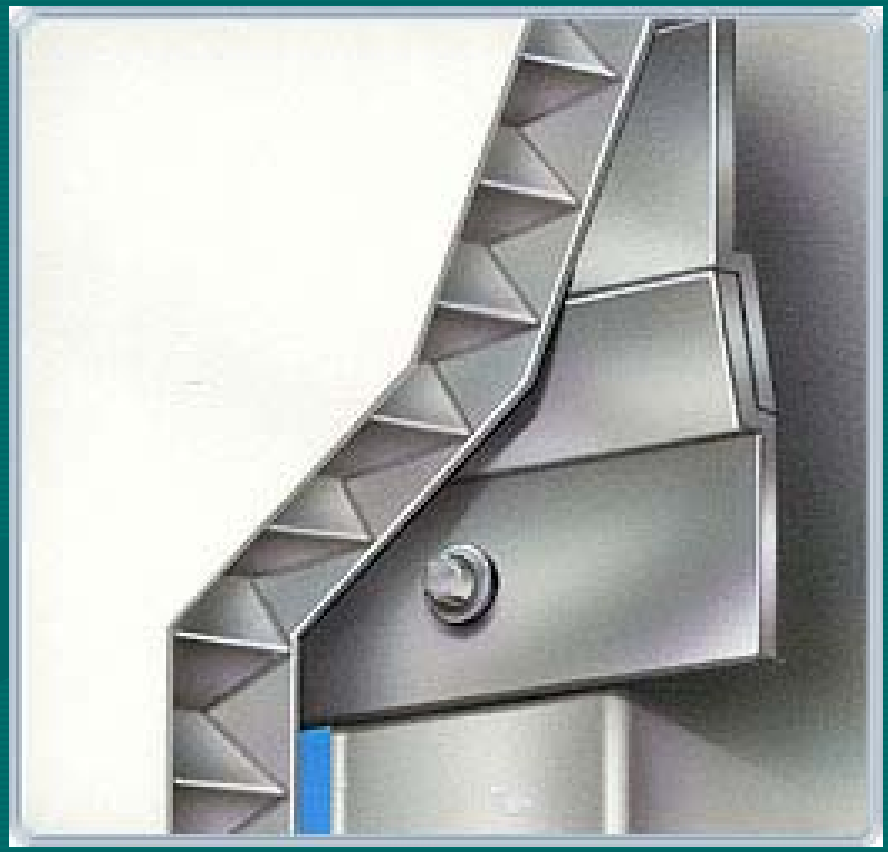
Modular Clean-room Facilities

- Pre-engineered, pre-fabricated walls and top decks that can support weight of air handling equipment, ceilings and filters.
- Can assemble relatively quickly in the field.
- One source for virtually everything for the cleanroom, airhandling, HEPA filters, wall panels, lighting, windows, doors, instrumentation and controls, all built into the package.
- Wall and ceiling systems typically of metal panels with special coatings that resist cleaning agents and give aesthetically pleasing look.
- Can opt for PVC finished panels or stainless steel finish panels also.

Materials of Construction & Surface Finishes
Modular Clean-room Facilities – Sample Manufacturer

PharmaWall System from PortaFab.

"Designed specifically for pharmaceutical and biotechnology facilities, the PharmaWall System utilizes a patent pending "Z" clip design that integrates with our 1/2" (12.7 mm) thick panels to be hung off a metal stud framework or an existing wall. The non-progressive system allows for the easy removal of panels. By connecting to a metal stud framework you no longer have to be limited with the depth of your utility chases. All piping, mechanical and electrical processes can be easily integrated within 3-5/8", 6", 12" or 18" cavities without having to create a "double" wall out of two free-standing partition walls."



Materials of Construction & Surface Finishes

Modular Clean-room Facilities – Sample Manufacturer

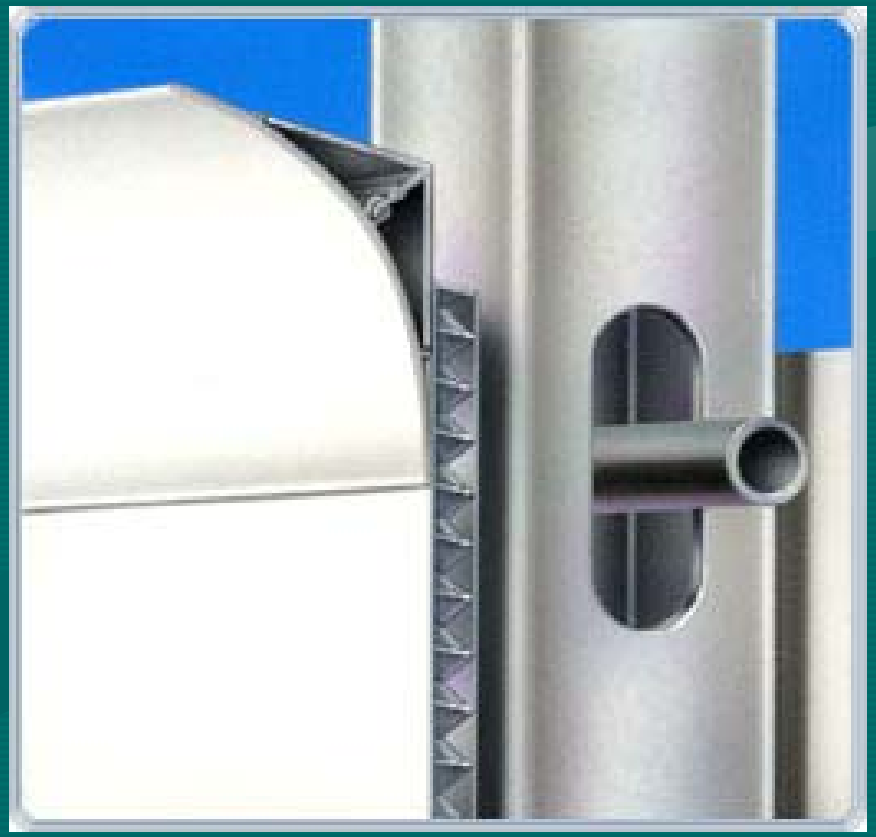
PharmaWall System from PortaFab.

Process & Utility Integration

"Piping penetrations and enclosures can be easily created by utilizing the PharmaWall system design. The radius cove details and cleanable surfaces meet the requirements for a clean space and allow for future piping expansion capability.

Process service panels are easily integrated into the PharmaWall system in a recessed manner that minimizes ledges and joints. The panels can be designed to allow maintenance access and provide for future piping expansion.

The PharmaSystem's modular design also allows cleanroom designers and contractors the ability to make field modifications during the installation process. This flexibility provides for a number of potential design cost savings."



Modular Clean Room Facilities:

- Reasons why modular construction may be used:
  - Compressed construction time
  - Flexibility for future changes
  - Other reasons:
    - Overcome local skill shortages
    - Reduced weight
    - Reduce number of contractors used during construction
      - Rely on the modular firm?
    - Pre-qualification testing and customer inspection of the facilities are completed before shipment to assure compliance.
    - Increased safety (Transferred to vendor?)

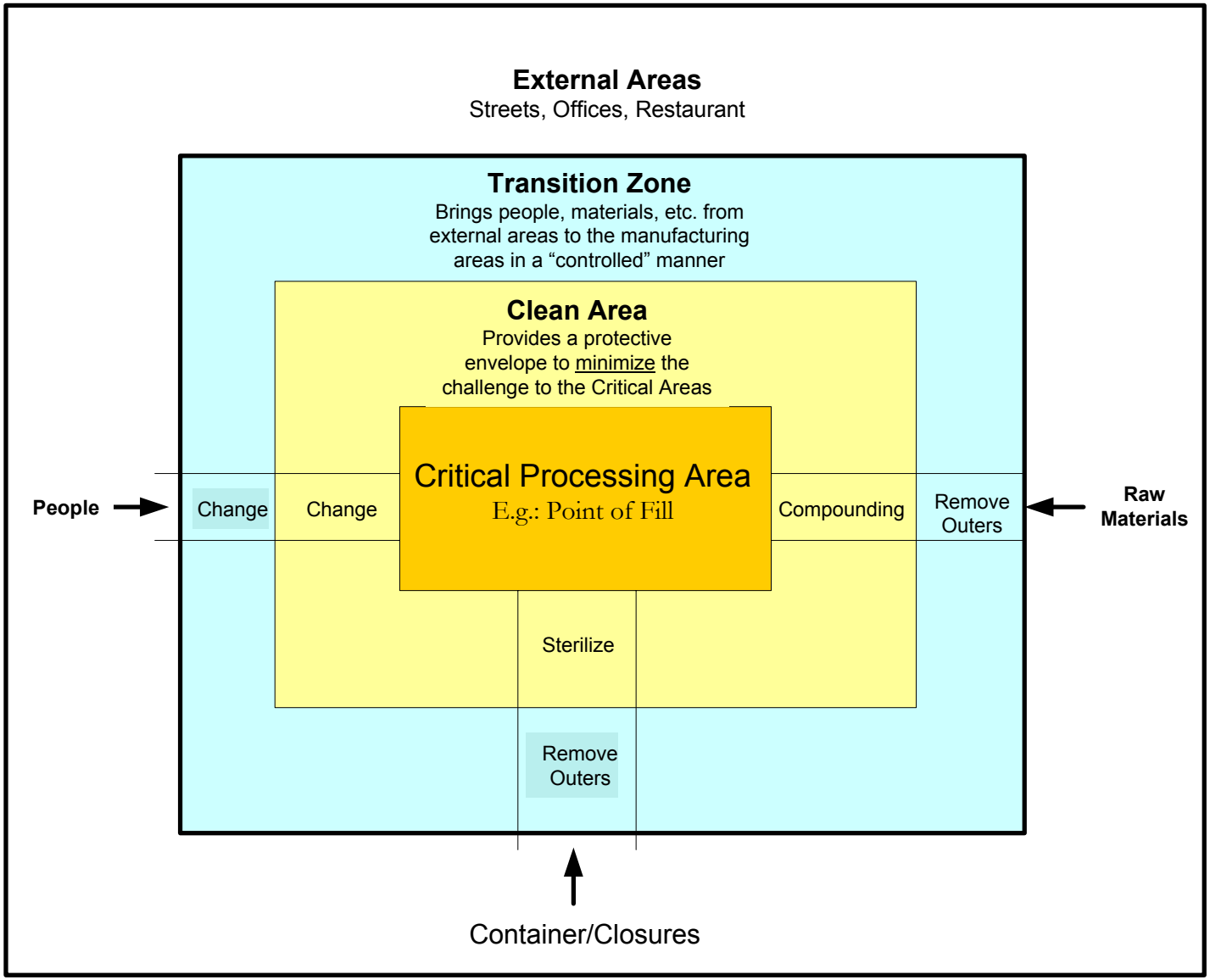
Modular Clean Room Facilities

Impediments to use of modular construction:

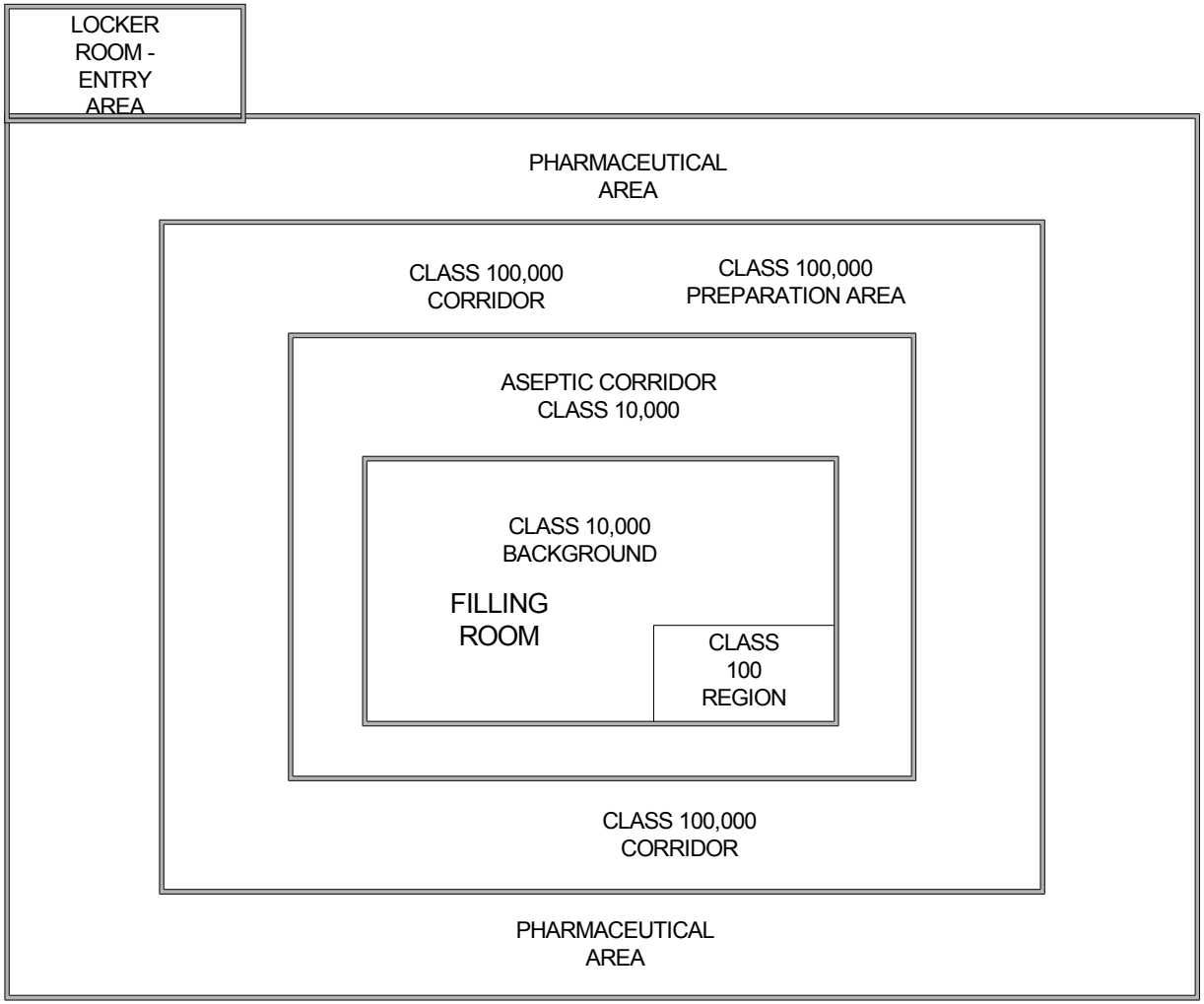
- Generally more expensive than the traditional "stick-built" clean room
- Increased engineering costs
- Early design freeze which may reduce flexibility of scope
- Complicated interface (coordination) issues
- Absence of a robust economic advantage
- Must complete flooring, sprinklers, and other utilities in the field (i.e.: water, electric, specialty gases, etc)

Room Pressurization

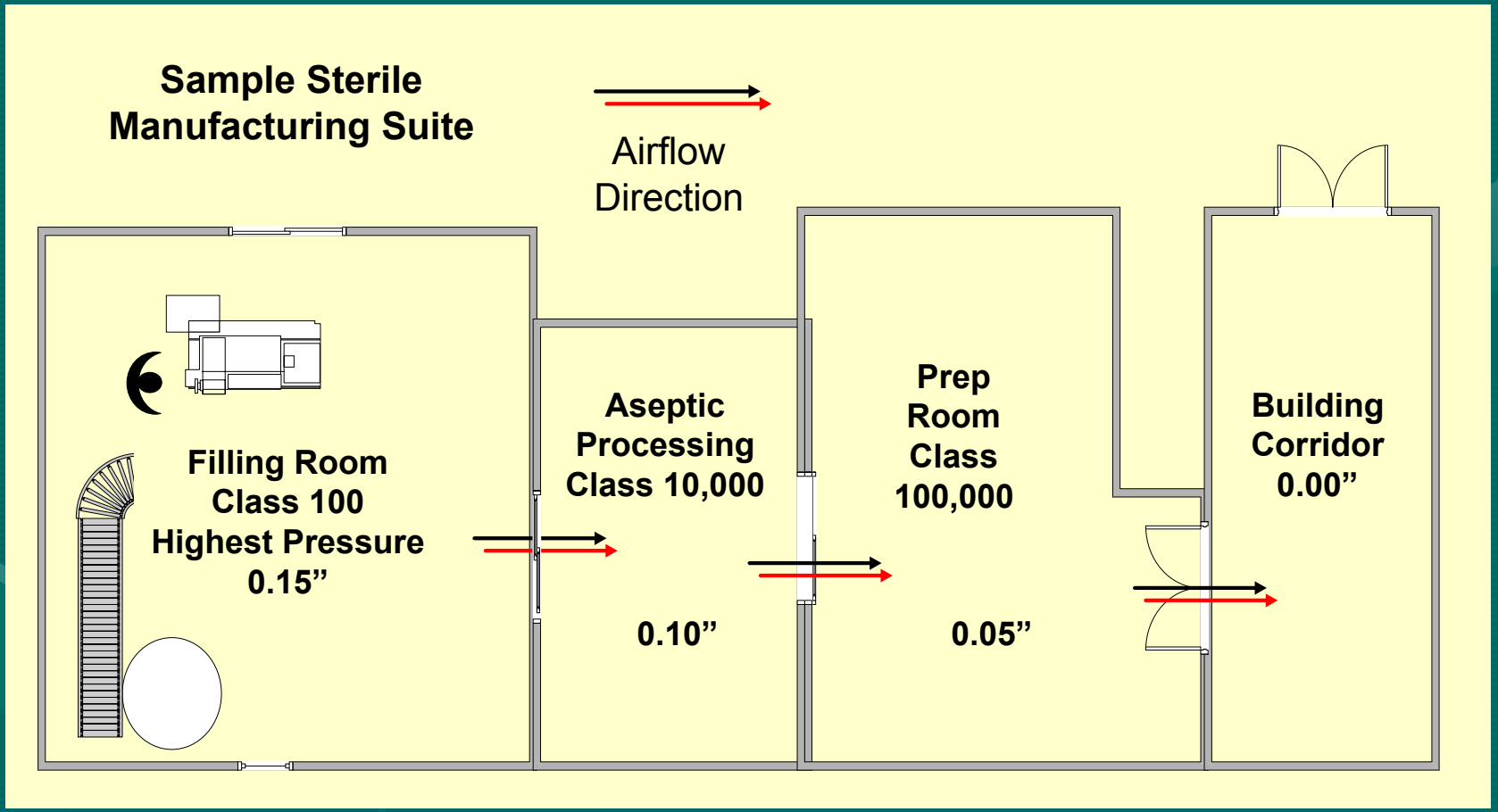
- Both US and EU requires that rooms of higher grade must be at higher pressure levels.
- Typically 0.05" water column difference between classes.
- Ensures air flows from cleaner areas to dirtier areas. Class 100 filling rooms always have the highest pressure.
- Class 100 fill rooms will sometimes have regions that are class 10,000 (there is no requirement to have the entire room at class 100) however the room is still considered a class 100 room in terms of pressure levels.

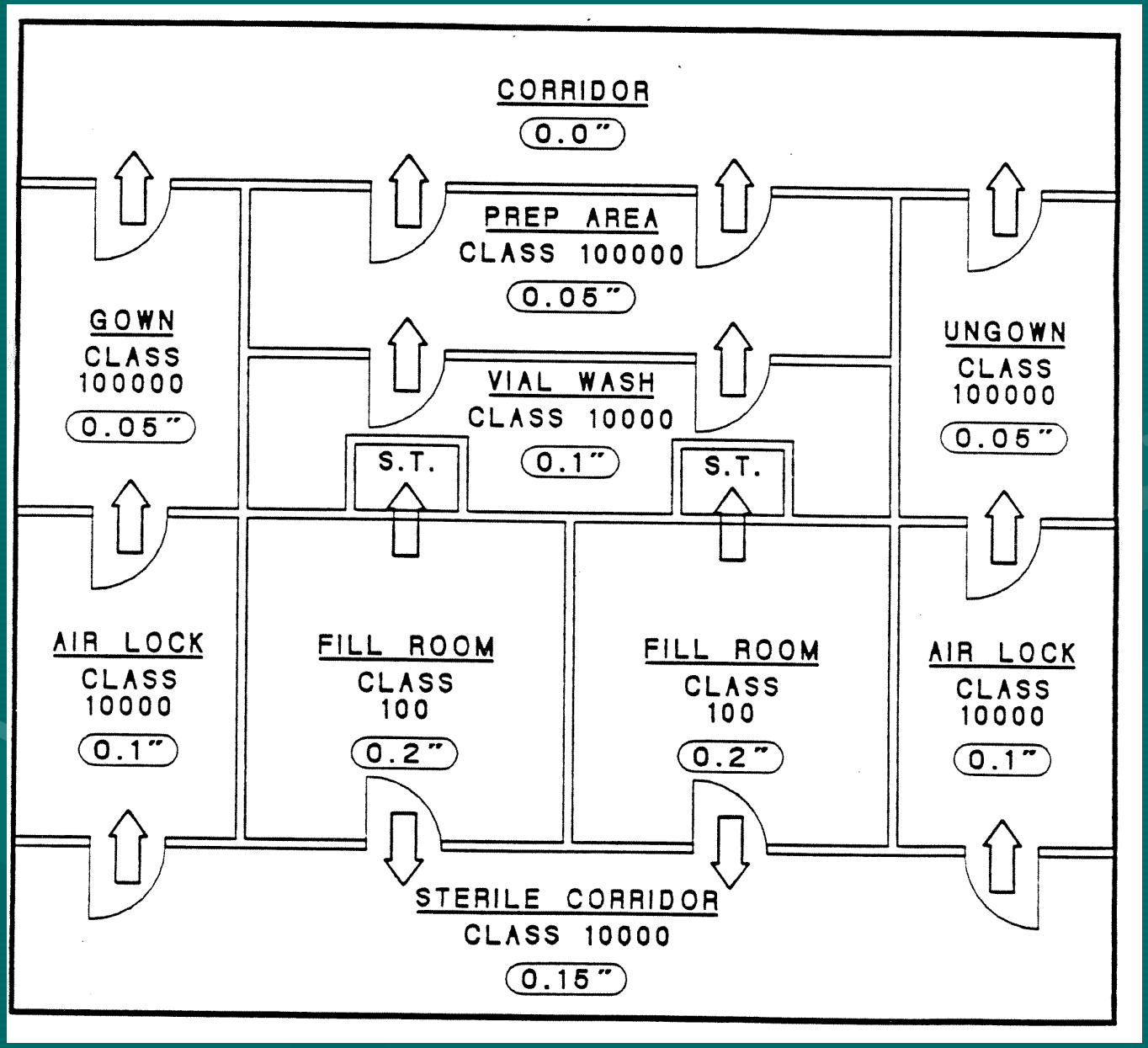

External Areas
Streets, Offices, Restaurant
Transition Zone
Brings people, materials, etc. from external areas to the manufacturing areas in a "controlled" manner
Clean Area
Provides a protective envelope to minimize the challenge to the Critical Areas
Critical Processing Area
E.g.: Point of Fill
People
Change
Change
Compounding
Remove Outers
Raw Materials
Sterilize
Remove Outers
Container/Closures

Classification Levels within an Aseptic Facility
Nested Manufacturing Zones (Five Zones)



Clean Room Pressurization - Example





Another example of cascading room pressures

Example of an actual facility layout