PhEn - 602
Semester Review

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Spring ‘09

From Notes # 1

Pharmaceutical Facility Design

Good Manufacturing Practice (GMP's)

Food, Drug and Cosmetic act gives FDA authority enforce legal requirements in manufacturing, processing, packing and holding of drugs.

- These requirements are found in

  21CFR Part 211

  Subpart C relates to "Buildings and Facilities"

Facility Planning is Critical

"Exceptional facilities don't just happen…they are planned to be functional, efficient, cost effective, and compliant to all regulations. They are planned to meet market demands for product…to be environmentally pleasing to those that work in them on a daily basis…and they are planned to be safe, protecting the workers and the outside environment."

From J. Odum, Sterile Product Facility Design and Project Management.

Facility Planning is Critical

Proper planning is the key.....having a sound project management process is crucial

In order to properly plan the facility, a significant amount of information is needed, such as project goals and objectives, product volumes, schedule, budget costs, utility requirements, safety requirements, etc., etc.
This information is typically gathered during the facility programming portion of the conceptual design phase.

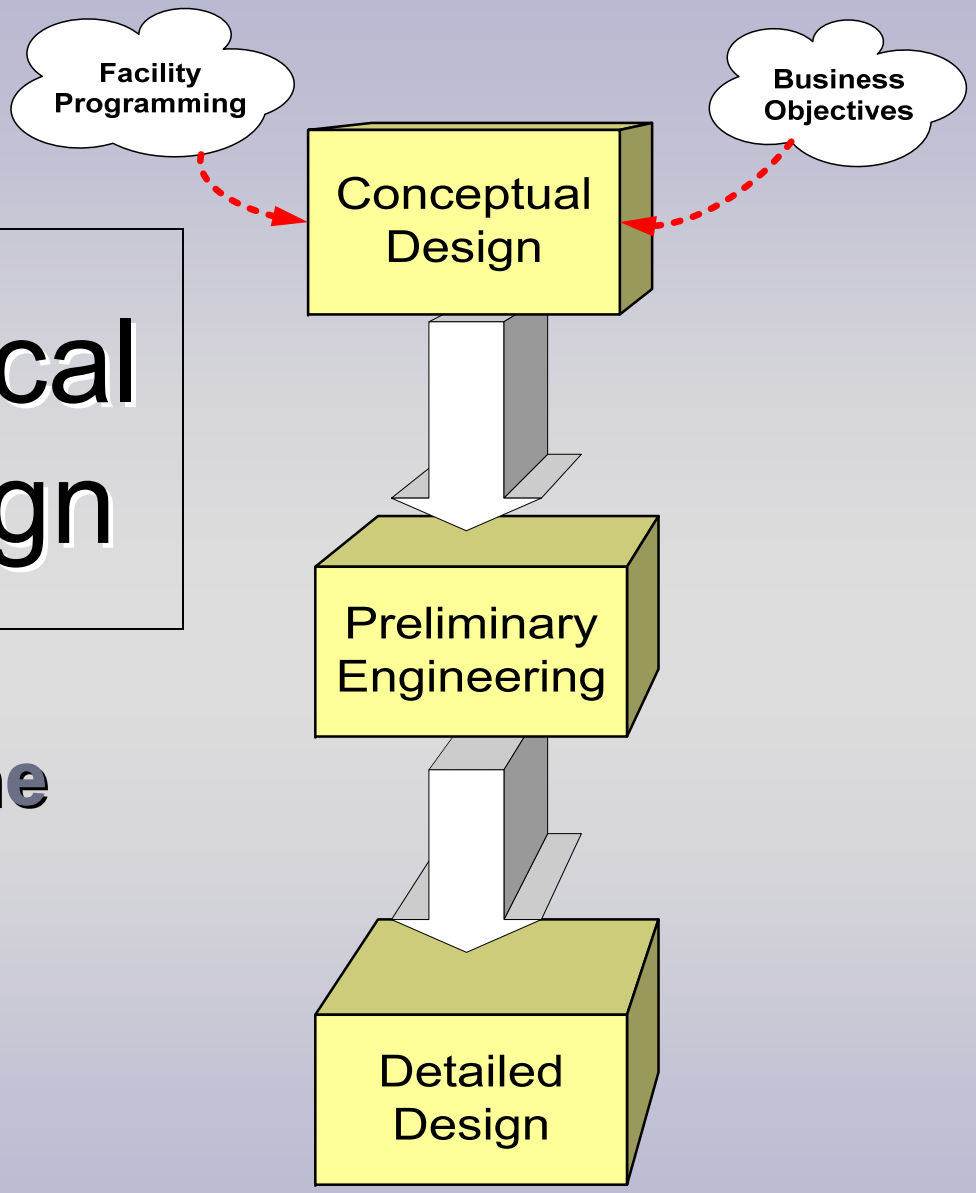
Pharmaceutical Facility Design

PhEn-602 focus:

- **Design (1,2 & 4) and**
- **Commissioning, Validation/Qualification(7 & 8)**
  1. **Conceptual Study**
  2. **Functional Design/Preliminary Engineering**
  3. Request for Funds Approved
  4. **Detailed Engineering**
  5. Procurement
  6. Construction
  7. **Commissioning**
  8. **Validation/Qualification**
  9. Turnover to owner

Pharmaceutical Facility Design

Three phases to the Design Process

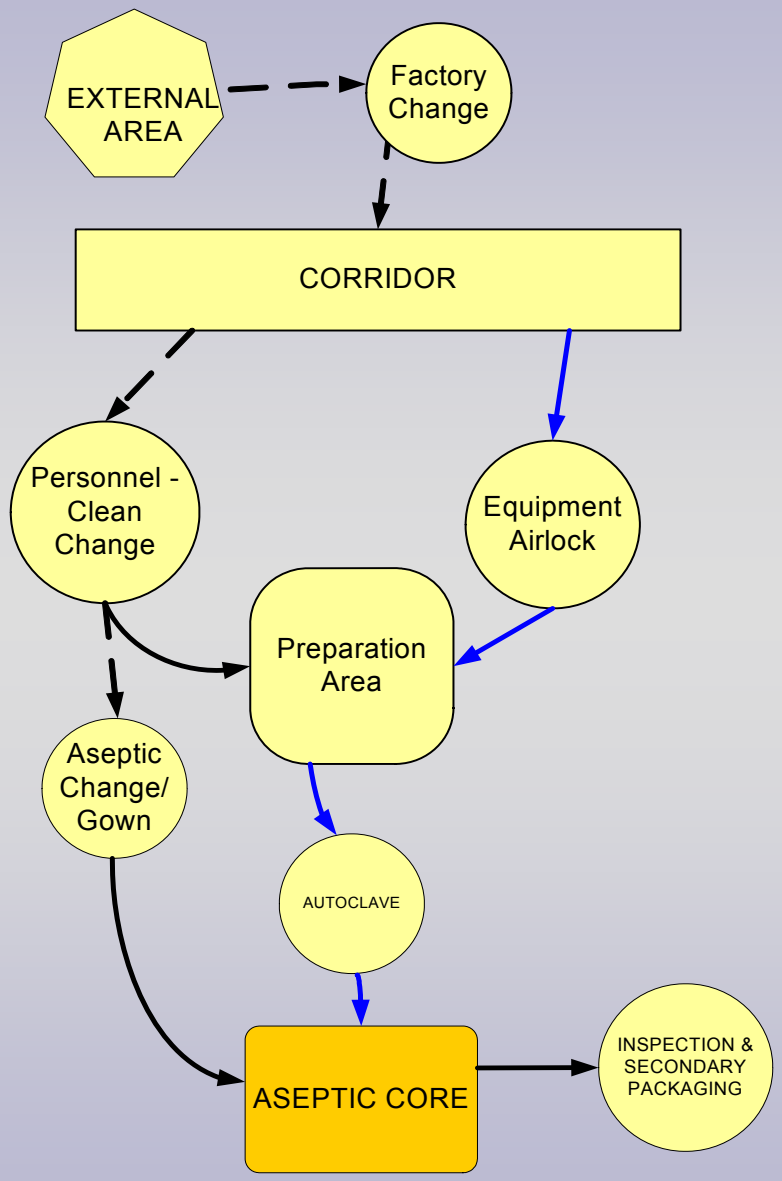


Conceptual Design-Basic Elements

- Establish goals and objectives – discuss how GMP requirements will be met
- Conduct facility programming – very important –involves extensive data gathering
- Conceptual layout and Accommodation Schedule
- Prepare “Basis of Design” (statement of criteria)
- Establish design philosophy: e.g. state-of the art or leading edge?
- Heating, Ventilation and Air-Conditioning Philosophy
- Major equipment list
- Budget estimate (often prepared for management review)

Conceptual Design Basic Elements:

1) **"Accommodation Schedule" also called "Bubble Diagram"**
2) **Defines adjacencies and high level flow of material and personnel**
1) **Performed prior to layout of area**



Commissioning

“A well planned, documented and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder expectations.”

Validation – An Essential Part of GMP

Validation is the scientific study of a system:

- To prove that the facility system/equipment is consistently doing what it is supposed to do (i.e., that the process is under control)
- To determine the process variables and acceptable limits for these variables, and to set-up appropriate in-process controls.

Validation as defined by FDA:

"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

Pharmaceutical Facility Design
Summary:

- **A structured project approach is required for successful implementation of Pharmaceutical Facility Projects**
- **A phased approach to the design is often used**
- **Good Engineering Practice and Commissioning play a key role in the project life-cycle**
- **Validation is an essential part of the facility system and must be considered at the earliest part of the project; during the design phase.**

From Notes # 2

International Code Council

- **International Code Council (ICC)** is a nonprofit membership association consisting of over 50,000 members dedicated to developing a single set of comprehensive model building codes. Most members are code officials.
  - http://www.iccsafe.org/
- **States adopt various codes from the ICC**

International Code Council

The mission of the International Code Council is to provide the highest quality codes, standards, products, and services for all concerned with the safety and performance of the built environment.

From International Code Council:

- **"The purpose of the Code is to establish the minimum requirements to safeguard the public health, safety and general welfare through structural strength, means of egress facilities, stability, sanitation, adequate light and ventilation, energy conservation, and safety to life and property from fire and other hazards attributed to the built environment".**

Construction Regulations - Building Codes

- Most Pharmaceutical Facilities fall under Use Group F: *Factory and Industrial Uses*
- Under use group F there are two further classifications:
  - F-1: Moderate hazard
  - F-2: Light hazard

Construction Regulations - Building Codes

What kinds of things are covered under the national building codes?

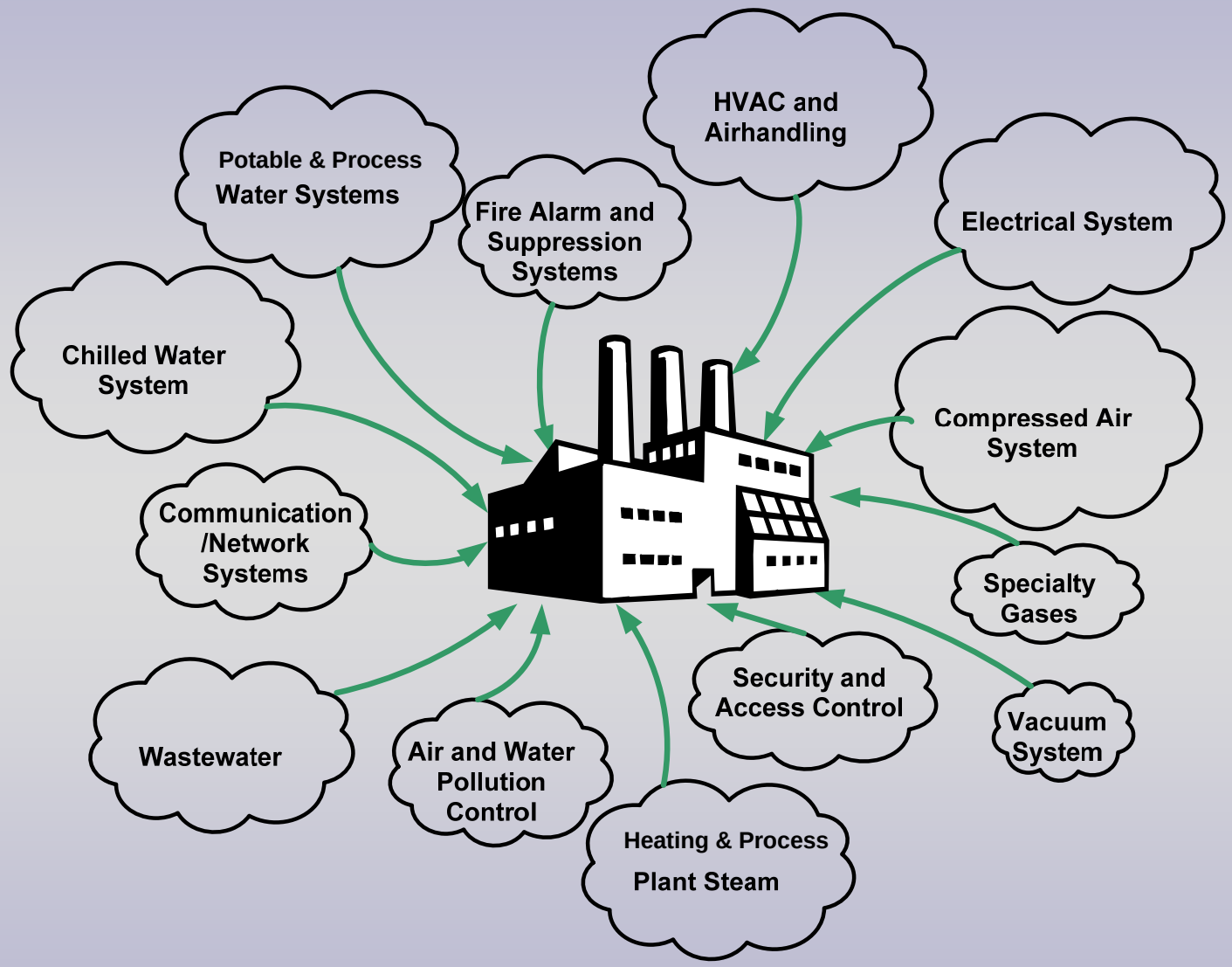
- Structural loads (roof loads, wind loads, snow loads)
- Means of egress (e.g. exits, stairway's, doorways,etc..)
- Fire resistive construction, fire walls
- Fire protection systems (e.g. sprinkler systems and smoke detectors)
- Foundation systems and retaining walls
- Mechanical systems, plumbing code

ALL ARE IMPORTANT CONSIDERATIONS IN THE DESIGN OF A PHARMACEUTICAL FACILITY

Construction Regulations - Building Codes

- *NFPA – National Fire Protection Association*
  - *NFPA 101 - Life Safety Code*
  - *Means of Egress*

Support Utilities & Facility Systems



Support Utilities:
Primary Steam for Heating

Heating Systems: Plant Steam

- High-pressure – typically 100 – 130 psig
- Low-pressure – typically 12 – 15 psig*
- Plays huge role in pharmaceutical facility systems
- Produced by boilers – many different types
- Boilers are rated in terms of boiler horsepower, convertible to lbs/hr of steam (1 BHP=34.5 Lbs/hr of steam)

Air Handling & HVAC Systems

Air Handler / Air Handling Unit: A unit designed to deliver a certain amount of air, typically consisting of a fan, filter assembly, dampers, heating and cooling coils, and control instrumentation.

- Come in all sorts of sizes, and materials of construction.
- Rated in terms of capacity, measured in CFM of air delivered by the unit.

Air Handling & HVAC Systems

Different grades of air handling units:

- Commercial grade – basic units serving commercial office buildings
- Industrial grade – more durable grade to serve manufacturing and other industrial areas
- Pharmaceutical grade – double wall construction, more stainless steel, lower leakage levels
- Some units are fitted with humidifiers and dehumidifiers

Support Utilities

Compressed-Air:

- Instrument Air
- Process Compressed Air
- Generated by air-compressors (Many Types)
- Distributed throughout the facility, typically in copper tubing.
- Measured in CFM (cubic feet per minute)
- Typically generated at 80 – 120 psig pressure

Support Utilities

Central Chilled Water Systems

- A distributed system that provides “chilled” water to air handlers and equipment
- Chilled water is created by chillers – many different types – based on refrigeration cycle
- Distributed throughout plant by pumps
- Temperature typically runs between 42° and 50° deg F.
- Fed to air handlers that provide air-conditioning for the building, for personnel comfort and environmental control
- In some cases, used directly by process equipment to provide cooling for the process

Support Utilities

Electrical Distribution

- **Must consider size and location of substation.**
- **Size and location of local motor control centers**
- **Must ensure design is consistent with all applicable codes (NEC)**
- **Consider if client desires on-site back-up generation**

Emission Control Systems Must be Considered by the Designer

Water:

- pH Control and Monitoring Systems
- Local sewerage authority has limits based on DEP requirements

Air (DEP Limits):

- Air emission control devices such as scrubbers and catalytic incinerators used to remove solvents (VOC's: Volatile Organic Compounds) from the air stream
- Dust collectors to pickup particulates.

Security & Access Control

- **Has to be considered during facility design**
- **Much more attention recently from Pharmaceutical Industry**
- **Must have a well-thought-out security plan**
- **Security systems need to be effective, but subtle**
- **Want employees focused on their job – don't want a fortress mentality**
- **Security Plan starts off with defining your critical assets**

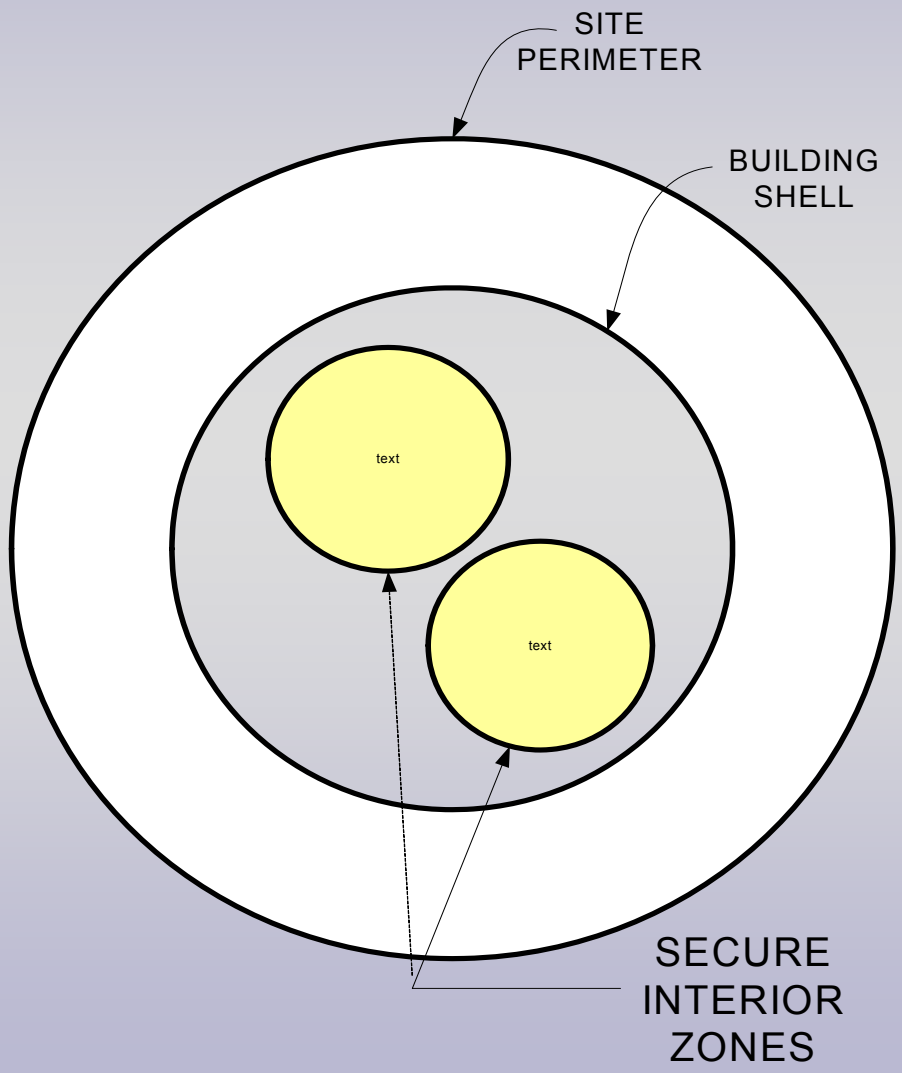
Security & Access Control

Fundamental Security Concept:

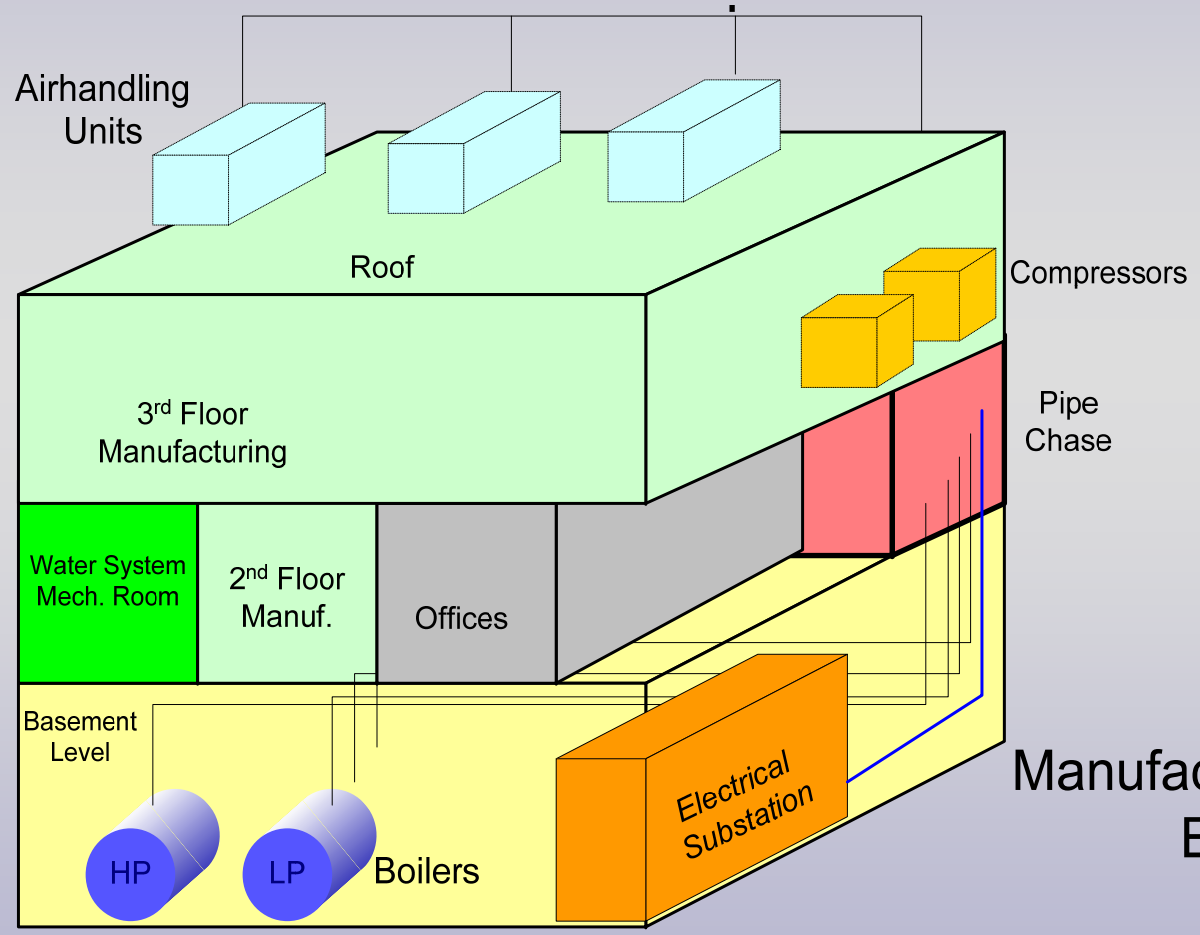
Concentric Rings of security

Increasingly more secure areas as you proceed toward the critical areas.

Each zone boundary has controls to prevent against threats.



Putting it all together – Visualizing the building and utility systems



Manufacturing Building Example

From Notes # 3

Definitions

Terminal Sterilization

A process by which the final sealed container (including product) is subjected to a sterilization process, such as heat or radiation.

Aseptic manufacturing

Aseptic Processing is a process that combines a pre-sterilized product with a presterilized container that is then closed with a presterilized closure in a clean room

Excerpt from FDA's Aseptic Guidelines: Aseptic vs. Terminal Sterilization

- In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together. Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment. Aseptic processing involves more variables than terminal sterilization.

Typical Steps – Vial Formulation:

1. Dispensing
2. Compounding
3. Filtration
4. Container Preparation
5. Stopper Preparation
6. Filling and Stoppering
7. Lyophilization
   A. For non-terminally sterilized products
8. Capping and Crimping
9. Terminal Sterilization
10. Inspection
11. Packing

Sterile Processing

Container Preparation

Two types of depyrogenation

Ovens typically employed:

- Batch oven: Vials are loaded onto cart and manually loaded and unloaded by operator (smaller quantities)
- Depyrogenation tunnel: Vials automatically fed and driven across a “tunnel” with hot air (larger quantities)

Sterile Processing

Component Sterilization

Components such as filter housings, filling pumps, and vibratory bowls, must be sterilized before use in the process. These parts are sterilized in an autoclave.

- Three primary types of autoclaves:
  - Steam: Saturated steam mixture in chamber contacts the materials
  - Air & Steam Mixture: Sterile compressed air and steam mixture
  - Water Cascade: Hot WFI “rains” over the material – not used for parts sterilization

Concern: Air must be evacuated. Air insulates and prevents lethality by saturated steam

Sterile Processing

- **Filling Operation:**
  - **MOST CRITICAL OPERATION**
  - ***Process by which the sterile filtered product is dosed into the washed and sterile, depyrogenated containers.***
- Note: Product contact parts must be sterilized before use ...e.g. filling pumps, vibratory bowls and guide rails, filling vessel.
- Minimize time of filling. Container must be sealed/closed **ASAP** after filling.

Sterile Processing

Lyophilization (Freeze Drying)

"Process of removing water by first freezing, and then freeze-drying to produce a stable product"

Popular process for preserving a wide variety of products

For lyophilized products:

- **Vials only partially stoppered**
- **Filled vials transported into a lyophilizer**

Sterile Processing

Main components of a lyophilizer

- Chamber
- Condenser
- Refrigeration and heating skid

Sterile Processing

Lyophilization Unique Issues:

- Refrigeration skid requires cooling, typically chilled water
- Very large equipment
- Very energy intensive
- Leaks are a major concern, since product is exposed and a deep vacuum is drawn
- Must have trained personnel due to the relative complexity of the equipment
- Requires very long cycles

From Notes # 4

Clean Rooms and Controlled Environments

Basic definitions

- Clean Room: A room in which the concentration of airborne particles is controlled and contains one or more clean zones
- Clean Zone: A defined space in which the concentration of airborne particles is controlled to meet a specified airborne particulate class.

Controlled Environments - Types of Contaminants

- Non-viable Particulates
  - Metal specks, fiber from clothing
  - Obtained from: Equipment, people, tools
- Viable (micro-organisms)
  - Bacteria
  - Yeast, molds
  - Obtained from: People, outside air, water, equipment, tools, excipients, active ingredients

Clean Rooms and Controlled Environments

Sources of particulate generation

- Internal:
  - Personnel
    - Normally the highest source of contamination
  - Process
  - Airconditioning system
  - Introduction of raw materials
  - Introduction of equipment and materials
- External
  - Outside air

Clean Rooms and Controlled Environments

Some more interesting facts:

- Smaller, "respirable" particles remain virtually suspended in the air until breathed in.
- Approximately 98-99% of all particles by count are in the size range of 5 microns or less. These particles tend to remain in suspension or settle out so slowly.

From: www.peakpureair.com/particlesize.htm

Personnel – Largest Source of Contamination

- People are huge sources of contamination - ***the biggest source of viable and non-viable contamination***
- Each adult loses about 6 - 14 grams of dead skin material every day
- Each person loses a complete layer of skin about every four days - equivalent to 10,000,000 particles per day!
- Ordinary walking movements emit about 10,000 particles per minute.

Clean Rooms and Controlled Environments

- Occupancy state of the cleanroom:
  - As-Built: As constructed, with no equipment or personnel in room
  - At-Rest: Equipment in room, but no personnel
  - Operational: (also called “In-Operation”) Personnel and equipment in room, under normal operations

Clean Rooms and Controlled Environments

FDA Aseptic Guidelines – 1987

Requires pharmaceutical companies to use the FS-209E classifications for aseptic manufacturing.

Non-viable particle levels must meet the FS 209E classes.

Concerned only with the “in-operation” condition.

Concerned only with particles greater than or equal to 0.5 microns.

Contains limits for viable particles also – to be discussed later.

Website: www.fda.gov/cder/guidance /old027fn.pdf

Clean Rooms and Controlled Environments

FDA Aseptic Guidelines – 1987

Controlled Area:

"A controlled area is one in which unsterilized drug product, in-process materials or containers/closures are prepared..... acceptable air quality if it has a per-cubic-foot particle count of not more than 100,000 in a size range of 0.5 micron and larger (Class 100,000) when measured in the vicinity of the exposed articles during periods of activity.

FDA Aseptic Guide – Class of CleanRoom

- **Supporting Clean Areas**
- The nature of the activities conducted in a supporting clean area determines its classification. ***FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards under dynamic conditions***. Manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5). An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities (e.g., equipment cleaning).

Clean Rooms and Controlled Environments

FDA Aseptic Guidelines – as mentioned:

Originally published in 1987

Revised - September 2004

"Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing"

http://www.fda.gov/cder/guidance/5882fnl.htm

These are Guidelines – not regulations

(21 CFR 210 and 211 are regulations/law).

However, as far as manufacturers are concerned, they are as important as the law, since it represents FDA's current thinking and expectations.

Section IV: Buildings and Facilities

*important guidelines re: aseptic facility design

Clean Rooms and Controlled Environments

Eight ISO standards originally conceived

- 14644-1 "Classification of Air Cleanliness" A*pproved*
- 14644-2 "Specifications for Testing and Monitoring to Ensure Continued Compliance with ISO 14644-1" *Approved*
- 14644-3 "Metrology and Test Methods"
- 14644-4 "Design, Construction and Start-up"
- 14644-5 "Operation"
- 14644-6 "Terms and Definitions" (dictionary) 14644-7 "Separative enclosures (clean air hoods, gloveboxes, isolators, mini environments)"
- 14644-8 "Molecular Contamination"

Clean Rooms and Controlled Environments

- **Must classify each clean room in terms of:**
  - ISO class
  - Occupancy state
  - Particle Size

Eg.: ISO Class 5 “as-built” at 0.2 and 0.5 micrometers

Clean Rooms and Controlled Environments

ISO 14644-1 gives a method to classify cleanrooms. The classification is based on the following equation:

$$C_n = 10^N (0.1/D)^{2.08}$$

- **Cn is the maximum permitted concentration (in particles/m^3 of air) of airborne particles that are equal to, or larger, than the considered particle size.**
- **Cn is rounded to the nearest whole number, using no more than three significant figures.**
- **N is the ISO classification number, which shall not exceed the value of 9. Intermediate ISO classification numbers may be specified, with 0.1 the smallest permitted increment of N.**
- **D is the considered particle size in mm.**
- **0.1 is a constant with a dimension of mm.**

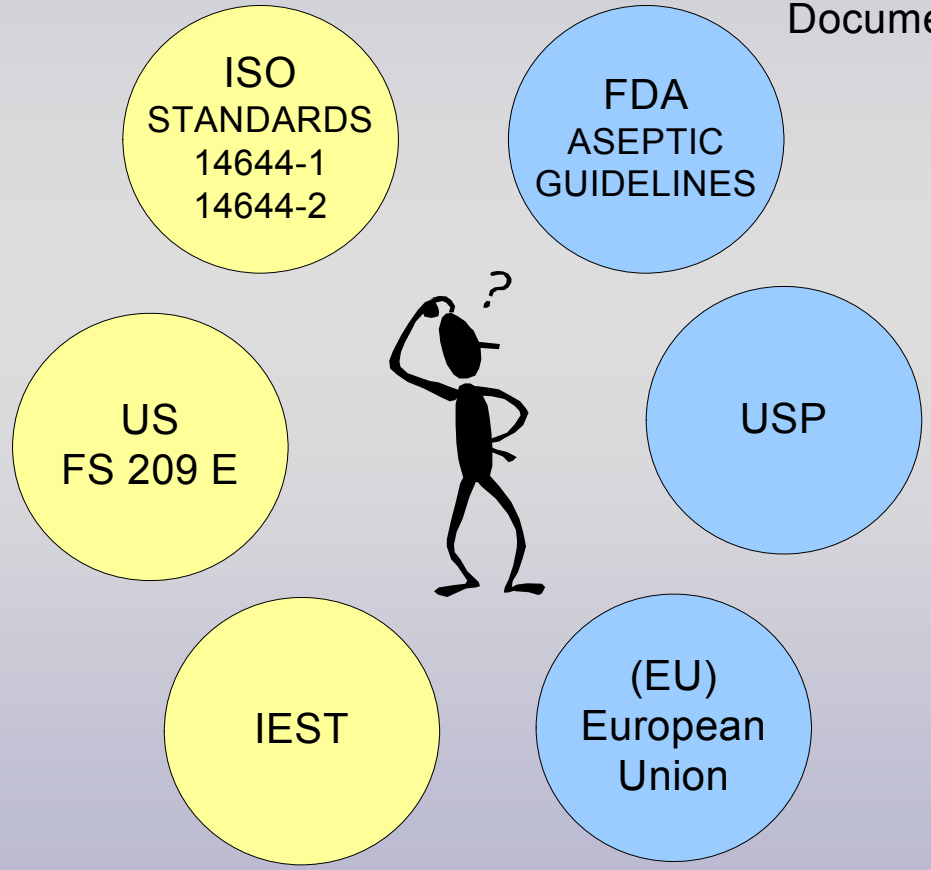
Clean Rooms and Controlled Environments – Cleanroom Standards

- FS 209E - US Federal Standard 209E
- ISO - International Standards Organization – the "NEW" standards –very important
- IEST- "Institute of Environmental Sciences and Testing"
- FDA Aseptic Guidelines
- EU - European Union GMP's
- USP - United States Pharmacopeia

Clean Rooms and Controlled Environments – Cleanroom Standards

General Standards

Pharmaceutical Regulatory/Guidance Documents



Clean Rooms and Controlled Environments
FDA Aseptic Guidelines

Important Notes:

- **FDA Aseptic guidelines do not allow averaging at a sampling site!**
- **Each discrete sample must be below the class limit.**
- **This is important, since you can pass ISO and FS 209E, and not meet FDA requirement.**
- **FDA aseptic guidelines still reference the FS 209E classes, as well as the ISO classes. They are allowing manufacturer too use either system for cleanroom certification.**
- **The Pharmaceutical Industry does not typically use Class 1 or Class 10 rooms. These designations are commonly used in the semiconductor industry.**

FS 209E and other particle size limits

AIRBORNE PARTICULATE CLEANLINESS CLASSES

Class limits are given for each class name. The limits designate specific concentrations (particles per unit volume) of airborne particles with sizes equal to and larger than the particle sizes shown*

Class Name**		Class limits									
		0.1 µm		0.2 µm		0.3 µm		0.5 µm		5 µm	
		Volume units		Volume units		Volume units		Volume units		Volume units	
SI	English***	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)
M 1		350	9.91	75.7	2.14	30.9	0.875	10.0	0.283	–	–
M 1.5	1	1 240	35.0	265	7.50	106	3.00	35.3	1.00	–	–
M 2		3 500	99.1	757	21.4	309	8.75	100	2.83	–	–
M 2.5	10	12 400	350	2 650	75.0	1 060	30.0	353	10.0	–	–
M 3		35 000	991	7 570	214	3 090	87.5	1 000	28.3	–	–
M 3.5	100	–	–	26 500	750	10 600	300	3 530	100	–	–
M 4		–	–	75 700	2140	30 900	875	10 000	283	–	–
M 4.5	1000	–	–	–	–	–	–	35 300	1000	247	7.00
M 5		–	–	–	–	–	–	100 000	2 830	618	17.5
M 5.5	10 000	–	–	–	–	–	–	353 000	10 000	2 470	70.0
M 6		–	–	–	–	–	–	1 000 000	28 300	6 180	175
M 6.5	100 000	–	–	–	–	–	–	3 530 000	100 000	24 700	700

Clean Rooms and Controlled Environments

- **Pharmaceutical:**
  - A controlled* area where personnel are required to be in a minimal amount of gowning. E.g.: Packing hall. Typical gowning consists of coat, hat and shoe covers

  *controlled term is used generically. It is different from the controlled area referenced in the 1987 Aseptic guidelines.

- **Pharmaceutical with local monitoring:**
  - A pharmaceutical area that has at least some portions designed as Class 100,000 at rest.

Clean Rooms and Controlled Environments

- **Pharmaceutical also called "Controlled Not Classified"**
- Often designed as EU Grade D

Clean Rooms and Controlled Environments

USP Considerations

- “Although there is no direct relationship established between the 209E controlled environment, it is generally accepted by scientists that airborne microorganisms in controlled environments can influence the microbiological quality of the intermediate or final products manufactured.....”

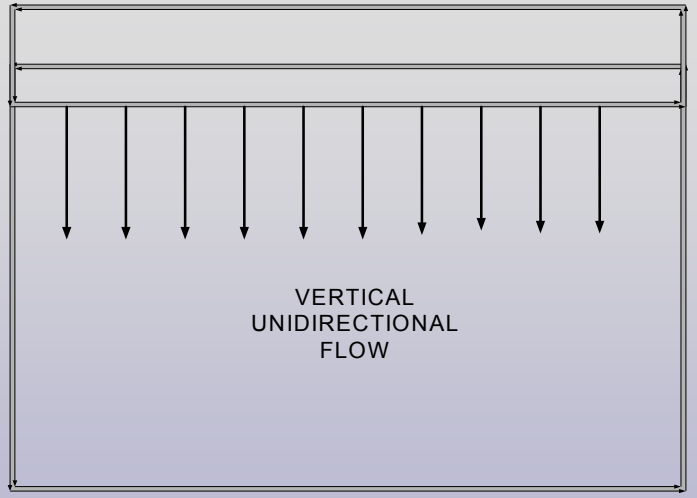
Controlled Environments

How do we reduce the level of contaminants?

- Airborne particles are HEPA filtered
- Contact parts are cleaned and sterilized
- Use of steam sterilization or irradiation of components
- Water purification systems are installed
- Limit aseptic core interventions
- Sterile filter the bulk solution (product)
- Wear clean room garments - limit shedding..follow proper aseptic techniques....very important.

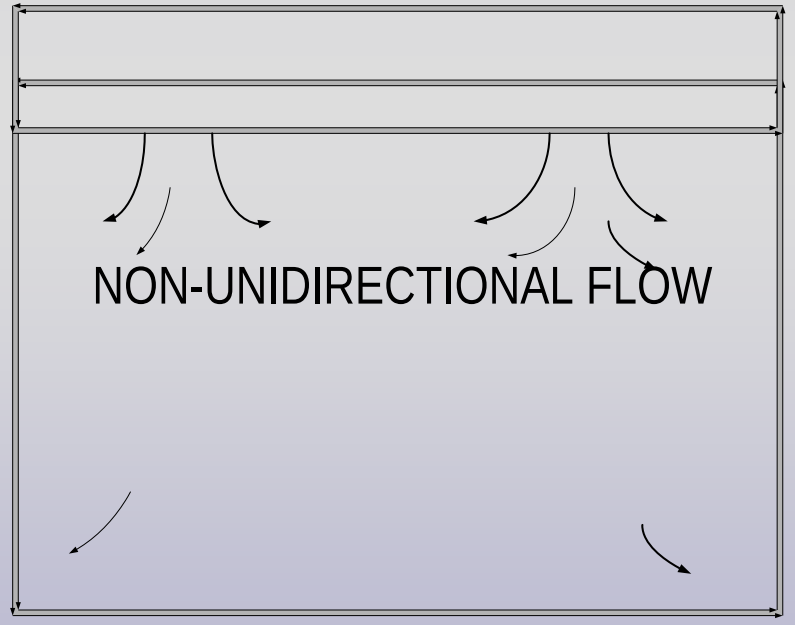
Clean Rooms and Controlled Environments

- Unidirectional Flow: Also called *Laminar Flow* – airflow having generally parallel streamlines, operating in a single direction, and with uniform velocity over its cross section. Eg.:



Clean Rooms and Controlled Environments

- Non-unidirectional Flow: Also called “mixed-flow” or “turbulent flow” – airflow which is not unidirectional.



Clean Rooms and Controlled Environments

ISO vs FS209E: key differences

- Three new classes were introduced; ISO Class 1 and Class 2, both of which are cleaner than FS 209E Class 1, & ISO Class 9.
- For the most part, ISO Class 3 through 8 are very similar to FS 209E Class 1 through 100,000.
- ISO added the 1.0 micron particle size
- ISO generally requires fewer sampling locations than FS 209E
- With ISO, number of sample locations is based on clean room area, whereas FS 209E it is based on Class, size of clean room, and whether or not unidirectional flow is present
- ISO has a minimum 1 minute sample time, FS 209E does not.

Clean Rooms and Controlled Environments

Common items: ISO Standard 14644-1 & 2 and FS 209E

- **No fewer than two sample locations**
- **If less than 10 samples are taken, *then use statistical methods*.**
- **Minimum sample volume and time is also dictated in each standard**
- **Averaging particle readings at a site is allowed. Two rules:**
  - **Acceptable as longs as average at each site is below the class limit.**
  - **Average of all sites should not exceed class limit, adjusted to 95% upper confidence interval…normal distribution assumed.**

Clean Rooms and Controlled Environments

Common items - ISO Standard 14644-1 & 2 and FS 209E

- **If less than 10 samples are taken, *then use statistical methods*.**
- **Averaging particle readings at a site is allowed. Two rules:**
  - **1. Acceptable as longs as average at each site is below the class limit,.**
  - **2. The 95% UCL (Upper Confidence Level) of the averages of all sites should not exceed the class limit.**

Clean Rooms and Controlled Environments

FS 209E & ISO Standard 14644-1 & 2

- **Sampling height is within 1 foot of equipment work surface area**
- **If no equipment present, typically 40” aff. is used**

  (aff.= above finished floor)
- **Note that the number of sampling locations is the minimum required.**
- **It’s often easier to sample a room at 10 or more locations, rather than going through the statistical analysis**

From Notes # 5

Clean Rooms and Controlled Environments

- European Union classifications – (this list excludes viable particulate limits)

	At-Rest		In-Operation	
	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)
	0.5μm	5μm	0.5μm	5μm
Grade D	3,500,000 (100,000)	20,000 (570)	No spec.	No spec.
Grade C	350,000 (10,000)	2000 (57)	3,500,000 (100,000)	20,000 (570)
Grade B	3,500 (100)	None	350,000 (10,000)	2000 (57)
Grade A	3,500* (100)	None	3500 (100)	None

Clean Rooms and Controlled Environments

ISO – number of sampling locations

- Particulate Testing - Number of sampling locations

$$N_L = \sqrt{A}$$

- N_L = minimum number of sampling locations
- A= area of clean room in square meters

Clean Rooms and Controlled Environments

ISO vs FS209E:

ISO 14644-1	FED Std 209E	
ISO Class	English	Metric
1		
2		
3	1	M1.5
4	10	M2.5
5	100	M3.5
6	1,000	M4.5
7	10,000	M5.5
8	100,000	M6.5
9		

Continuous Particle Monitoring Systems

- **Particle counting: continuous sampling**
  - **two types**
    - **Sequential monitoring system (manifold system)**
    - **Simultaneous monitoring system**

Clean Rooms and Controlled Environments

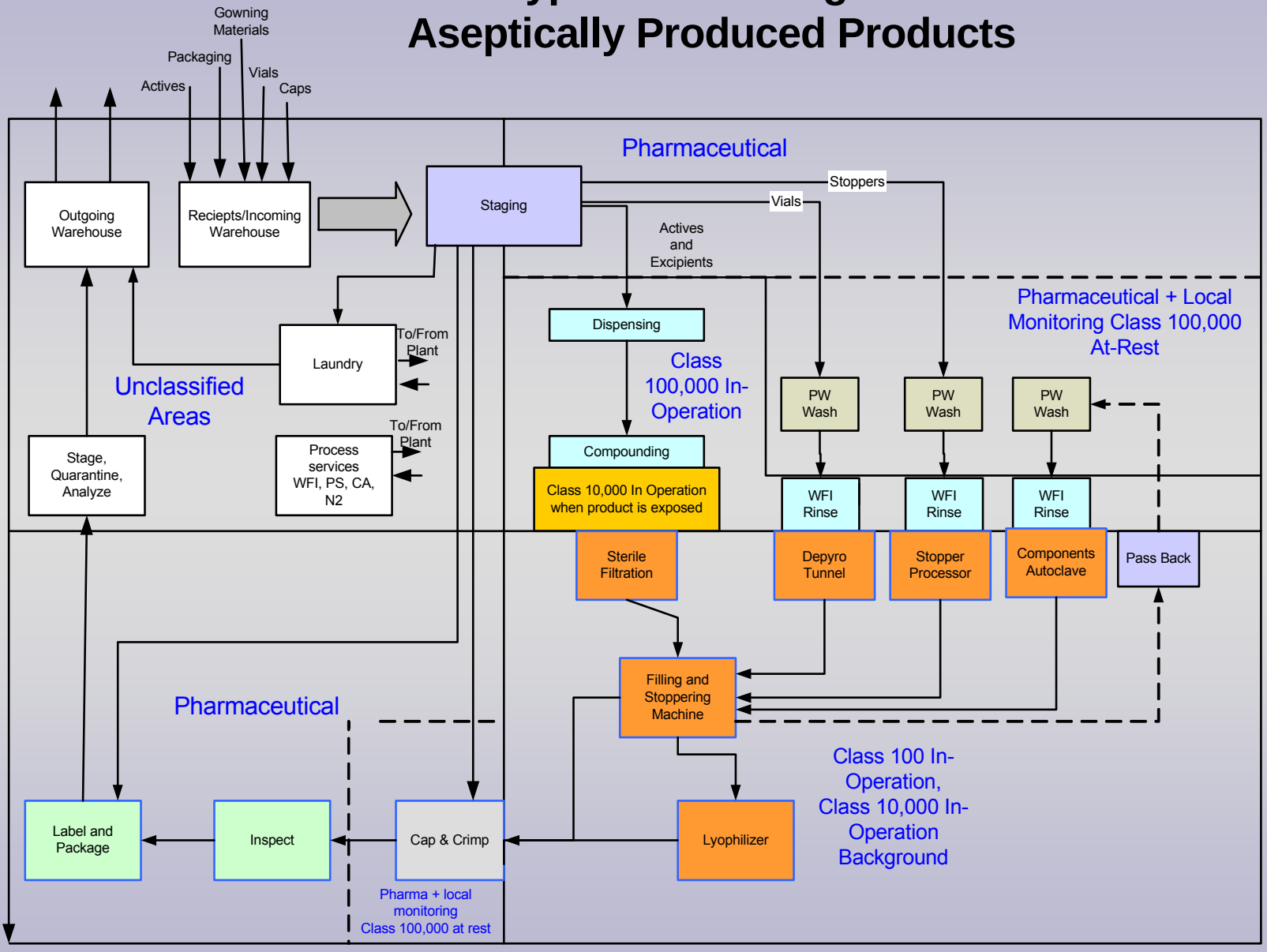
European Union Guide to GMP (EU cGMP)

- **"Grade A: The local zone for high-risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar flow work station. Laminar flow air systems should provide a homogeneous air speed"…**
- **"Grade B: For aseptic preparation and filling, this is the background environment for Grade A zone."**
- **"Grade C and D: Clean areas for carrying out less critical stages of the manufacture of sterile products."**

Summary of Grades and Classes vs. Process

Type of Processing	Process Step/Activity	Nearest equivalent ISO 14644-1 class "in operation"	US GMP expectation "in operation"	EU GMP Grade
Aseptic	Aseptic formulation and filling operations	5	100/M3.5	A
Aseptic	Background to the above activities	7	10,000/M5.5	B
Aseptic	Preparation of solutions to be filtered	8	100,000/M6.5	C
Aseptic	Component handling after washing when exposed to the environment	8	100,000/M6.5	C
Terminally sterilised	Filling of "unusually at risk" products	5	100/M3.5	A
Terminally sterilised	Filling of products, "unusually at risk" solution preparation	8	100,000/M6.5	C
Terminally sterilised	Preparation of products and solutions	unclassified/ controlled	Pharmaceutical	D

Typical Flow Diagram
Aseptically Produced Products



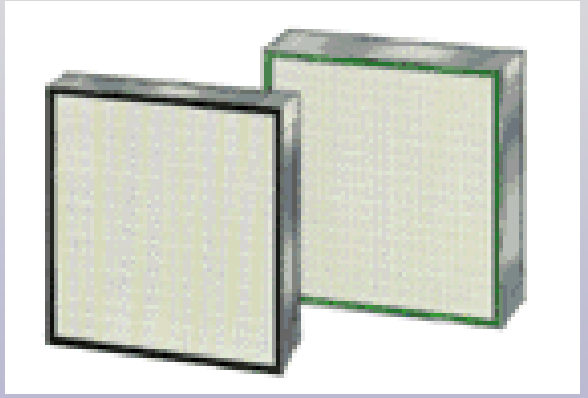
High Efficiency Air Filtration

- HEPA filters
  - Typically 99.97% efficient at 0.3 micron
  - Used for Clean Room Classes 100,000 thru 100
  - For Class 10 and better, use ULPA filters, Ultra Low Penetration Air filters
- ULPA Filters
  - Have an efficiency greater than 99.999% against 0.1 – 0.2 micron particles.

High Efficiency Air Filtration

Areas where leakage can occur:

- Housing to filter seal
  - Very important potential leak source
- Filter paper
- Filter paper to case cement area
- Frame joints
- Gasket



Clean Rooms and Controlled Environments
Summary of Tests for Cleanroom Certification

Seven primary tests:

1. Airflow Volume
2. Air Change Rate Calculations
3. Air Velocity Testing:

   (For a unidirectional flow clean room, it is velocity that is critical)

   Airflow direction between clean rooms: air should travel from cleaner room to less-clean room
4. Room to Room DP Testing
5. Filter Installation Leak Testing:

   To ensure no contaminants from the air system enter the clean room
6. Airflow pattern test (smoke test):

   Airflow direction within the clean room: air should flow from clean portion of room to dirty portion and then be extracted
7. Particle count testing

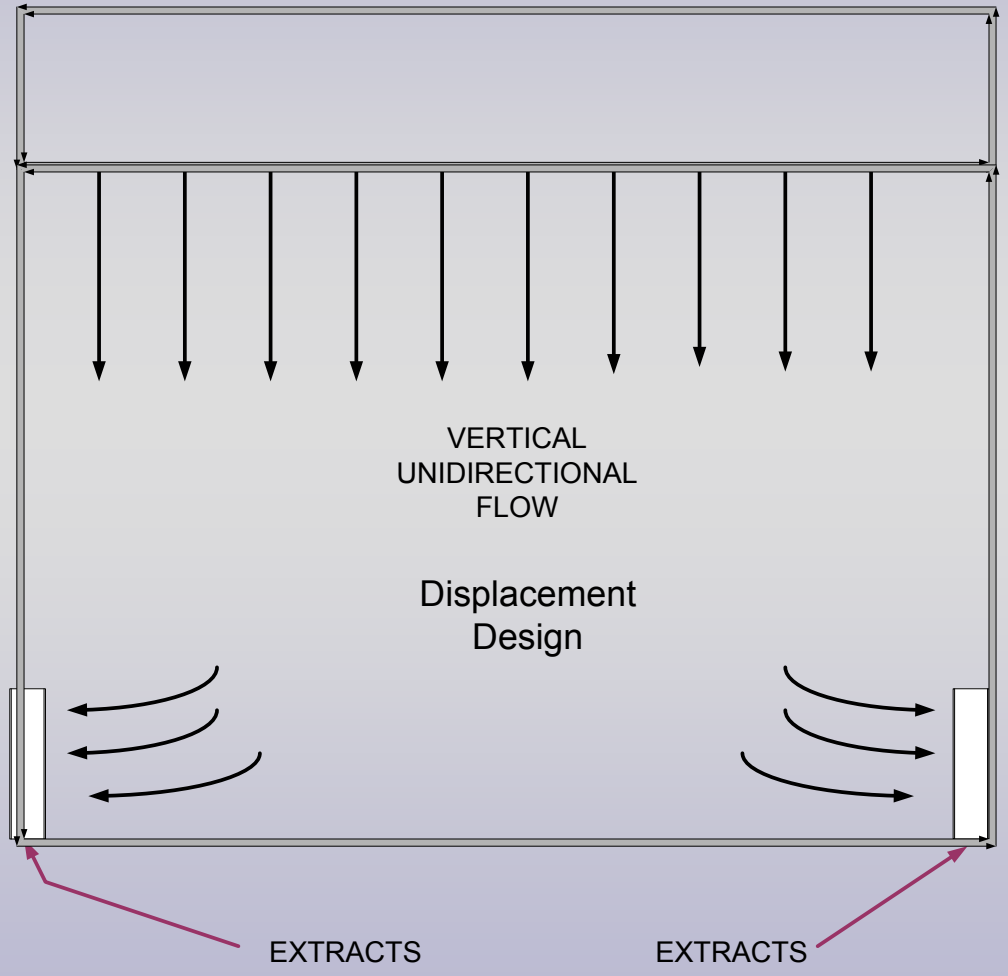
Clean Rooms and Controlled Environments

Clean Room Design Principles

Displacement Design:

- Dirty air is displaced by clean air, travelling at a relatively high velocity
- Typical of unidirectional flow clean rooms (Class 100 rooms, EU Grade A rooms).

Displacement Design



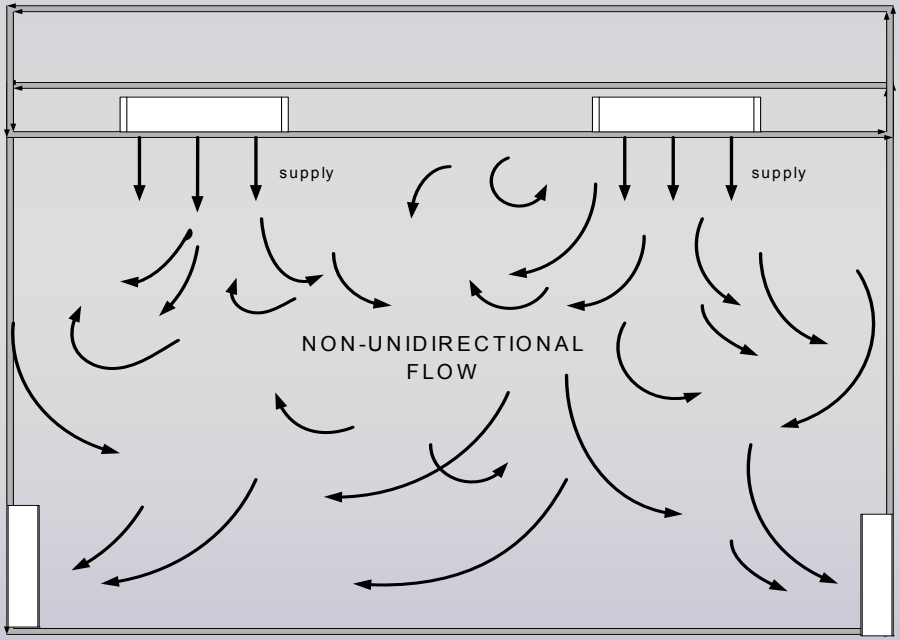
HVAC Design Principles

Dilution Design:

- "Dirty" air is mixed continuously with "clean" air.
- Turbulent air mixing – reduces the particulate load in the room.
- Typical of Class 10,000 and Class 100,000 rooms
- Dilution rooms are called mixed flow rooms
- Often have local regions in the room with displacement features

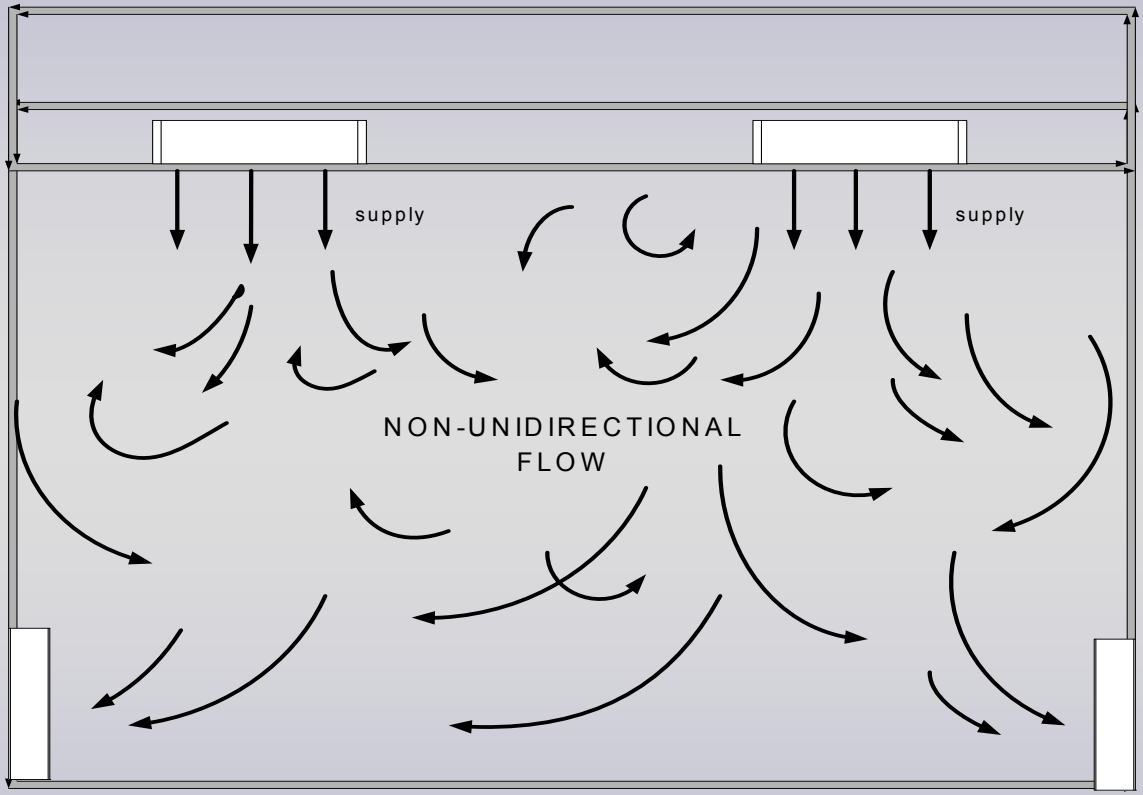
- Dilution Design: Non-unidirectional Flow:

  Also called “mixed-flow” or “turbulent flow” - airflow which is not unidirectional.



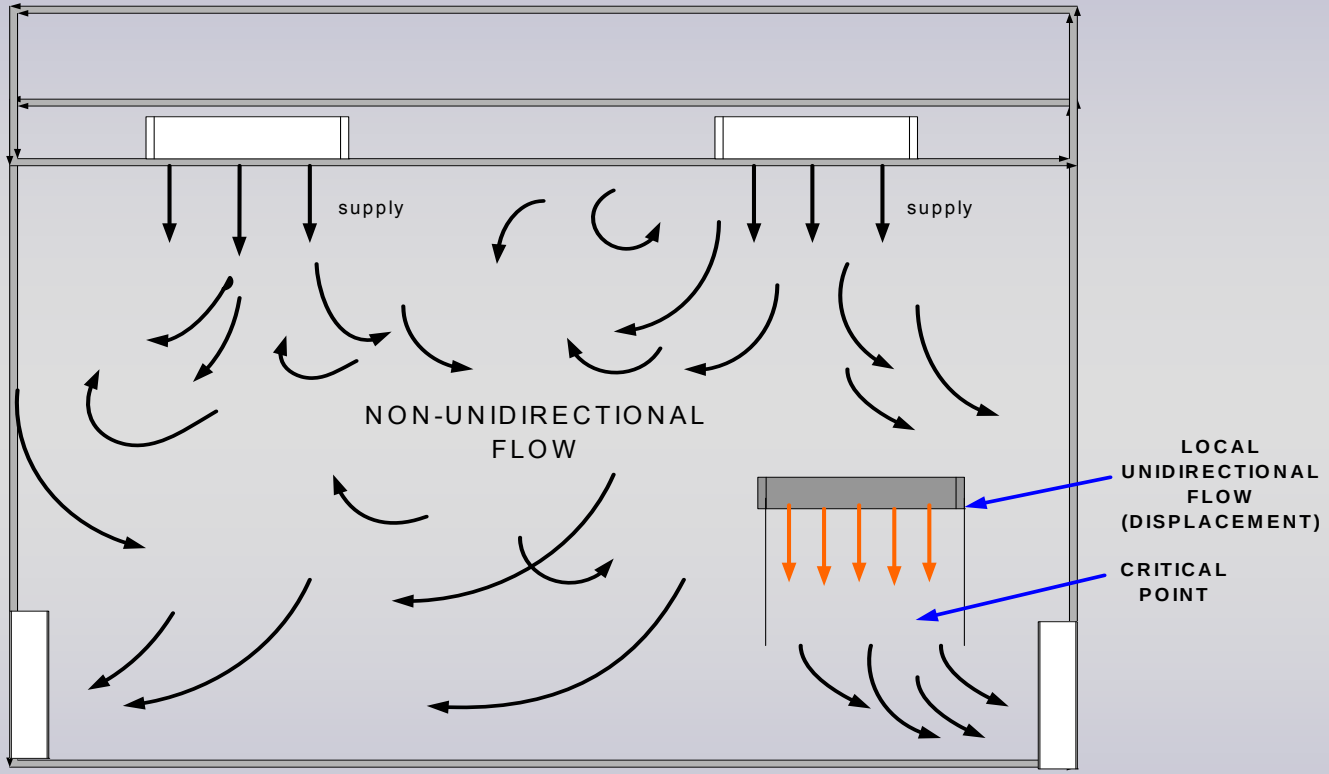
Example of a Dilution Design room

Dilution Design Room



Example of a
Dilution Design
room

Dilution with Local Unidirectional Zone



Example of a Dilution Design room

HVAC Design Principles

Unidirectional Flow (Displacement) Cleanrooms vs. Non-unidirectional Flow (Dilution) Cleanrooms

- Can generally achieve Class 10,000 with dilution design. In some cases even Class 1,000 is achievable.
- Higher cleanliness classes (i.e. cleaner than Class 1,000) requires unidirectional flow.
- Unidirectional Flow Cleanrooms have higher flow rates and as a result are more expensive to build
- Many more HEPA filters used with higher material costs

Clean Rooms: Airflows and Air Change Rates

- Minimum airchange rate for Class 100,000 clean rooms: **20 ACPH**
- What dictates this?

  1987 FDA Aseptic Manufacturing Guidelines
  2004 FDA Aseptic Manufacturing Guidelines
- There is no clear criteria for minimum air change rates for Class 1,000, 10,000 or Class 100
- There are targets however, from IEST.

Clean Rooms: Airflows and Air Change Rates

IEST recommended air change rates

RP-CC-012.1:

- Targeted airchange rates:
  - **Class 100,000** **5 – 48[1] ACPH** **ISO Class 8**
  - **Class 10,000** **60-90 ACPH** **ISO Class 7**
  - **Class 1,000** **150-240 ACPH** **ISO Class 6**
  - **Class 100** **240 – 480[2] ACPH** **ISO Class 5**

Important Notes:

1. Minimum air change rate for Class 100,000 rooms is 20 ACPH per 2004 FDA Aseptic Guidelines.
2. Air change rates for Class 100 rooms typically exceed 480 ACPH.

Clean Rooms: Airflows and Air Change Rates

- Airflow Velocity Specifications
  - No spec for Class 100,000, 10,000 or 1,000
  - Target for Class 100 Rooms:

90 Ft/min +/- 20%

Where does this requirement come from?

- **1987 FDA Aseptic Manufacturing Guidelines**

Clean Rooms: Airflows and Air Change Rates

- ***Air change rate should be based on satisfying the maximum particle load, based on the specific operation performed.***
- Varies depending on:
  1. ***Operation: Amount of particles generated in the space***
  2. ***Heat gain within the space***
  3. ***Required recovery time***

  Any of the above can determine the minimum air change rate.

  Calculating air volume to offset heat gain is a standard HVAC system design issue.

Clean Rooms: Air Change Rates per FDA

2004 FDA Aseptic Guidelines, section 4, part c:

"Air change rate is another important cleanroom design parameter. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas".

Unidirectional Flow Clean Rooms and air velocity

Air velocity in unidirectional clean rooms:

- Generally maintained between 60 fpm and 120 fpm
- For critical area: In the 1987 Aseptic Guide, FDA used to suggest 90 fpm +/- 20%.
- New FDA Aseptic Guide in 2004 changed this – they do not specify a target velocity or range.
- EU guidelines indicate 0.45 m/sec velocity, +/- 20% (guidance value). This equates to 0.36 – 0.54 m/s, or 70 fpm – 105 fpm.

Sample Problem

1. A firm is interested in determining whether the room meets ISO Class 3 requirements for the 0.3 micron particle size.
2. Is it necessary to perform statistical analysis to make this determination?
3. What is the 95% UCL?
4. Does the room meet ISO Class 3 conditions at 0.3 micron?
5. If the room dimensions were 5 m by 5 m, were the minimum number of sample locations per ISO met?
6. Does the room meet ISO Class 3 conditions for the 5 micron particle?
7. Does the room meet ISO Class 5 conditions for the 5 micron particle?
8. If the entire room was desired to be maintained at the required class for filling operations, and the readings were actually taken in the "in-operation" state, would the room meet EU requirements for filling operations for an aseptically produced product? (Assume unidirectional flow is provided).

From Notes # 6

Unidirectional Flow Clean Rooms Velocity Testing

- During qualification, airflow pattern tests/smoke studies should be performed to establish the acceptable velocity range.
  - Where is velocity measured?
    - **Filter face?**
    - **6” down?**
    - **Work level?**
  - For homework

Microbiological Considerations

- FDA Aseptic Guidelines: first document to establish general micro limits
- USP and EU GMP's provide more specific limits for micro-contaminants in the *Clean Room* in three areas:
  - Airborne
  - Surface
  - Personnel

Microbiological Considerations

- People are often the only source of micro-organisms or viable particulates in the clean room
- Micro-organisms are continually dispersed from people in the room
- Testing for microorganisms in the “as-built” or “at rest” state is of little value.

Microbiological Considerations

- Other sources of microbial contamination:
  - Water
  - Gases
  - Raw materials

- Important to monitor micro levels in these systems as well as air
  - Will not be discussed in PhEn-602

Microbiological Considerations

- Unit of measure is colony forming unit (cfu) (Viability?)
- FS 209E and ISO 14644-1 do not contain any specific limits for microbial contaminants
- ISO: Developing new standards for Micro limits in clean rooms

Critical Areas

- Critical Areas (sites, zones, surfaces) are identified as those areas where sterilized product or container and/or closures are exposed to the environment
  - Critical sites, zones, surfaces should be monitored most rigorously
  - Class 100 areas (EU Grade A)
  - **Organisms recovered from critical areas should be identified to genus and species for possible investigation**

Critical Area Examples:

- Room air in areas with product or container exposure
  - Path of any open containers
- Manufacturing equipment surfaces
  - Component loading areas
  - Filling Stations
- Storage containers
- Gloved hands
- Aseptic connections

Microbiological Considerations

1987 FDA Aseptic Guideline Limits:

- **Controlled areas: (Class 100,000 areas)**
  - **"with regard to microbial quality, an incidence of no more than 25 colony forming units per 10 cubic feet is acceptable."**
- **Critical areas: (Class 100 areas)**
  - **"air should also be of a high microbial quality....no more than 1 colony forming unit per 10 cubic feet is considered attainable and acceptable".**

FDA Aseptic Guidelines: Clean Room Class

TABLE 1 - Air Classifications	CDER Aseptic Guidelines - 2004			
Clean Area Classification (0.5 micron particles/ft^3)	ISO Designation	G.T. or equal to 0.5 micron (particles/m^3)	Microbiological Active Air Action Levels (cfu/m^3)	Microbiological Settling Plates Action Levels (diam. 90mm, cfu/4 hours)
100	5	3,520	1	1
1,000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

Microbiological Considerations

- EU Limits for Microbial Contaminants
  - Differs for Grades A, B, C, D
  - No requirements for the “at rest” state
  - Requirements for
    - Airborne
    - Surfaces
    - Personnel Gowns
    - Personnel Gloves
  - EU has limits for surfaces contained in Class 100,000 areas. FDA & USP do not

Microbiological Considerations

- EU Limits for Microbial Contaminants
  - Airborne:
    - Grade A: less than 1 cfu/cubic meter
    - Grade B: less than 10 cfu/cubic meter
    - Grade C: less than 100 cfu/cubic meter
    - Grade D: less than 200 cfu/cubic meter

Microbiological Considerations

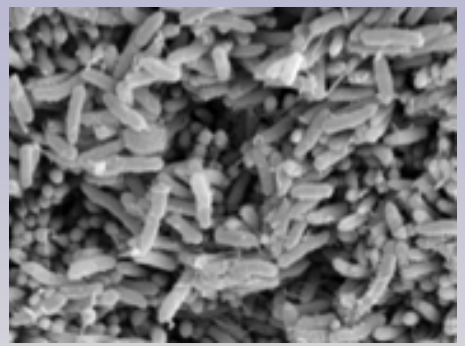
- USP Limits for Microbial Contaminants
  - Controlled areas: (Class 100,000 areas)
  - Class 10,000 Areas (sometimes referred to as “sub-critical” areas)
  - Critical areas: (Class 100 areas)

USP Airborne Viable Limits

Room Classification	cfu/m^3	cfu/ft^3
Class 100	<3	<0.1
Class 10,000	<20	<0.5
Class 100,000	<100	<2.5

Note: These limits are consistent with the 1987 FDA guidelines for Class 100, and Class 100,000 areas

USP Surface Limits



Class	cfu/contact plate (24-30cm^2)
100	3 (including floor)
10,000	5 10 (floor)

USP Limits for Personnel

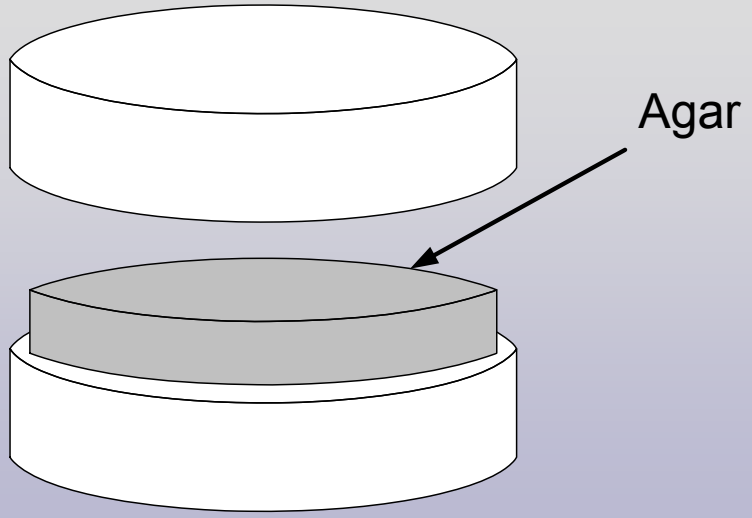
Class	cfu/contact plate Gloves	cfu/contact plate Garb
100	3	5
10,000	10	20

Environmental Monitoring

- EM Objectives
  - Monitor the effectiveness of the cleaning and sanitization
  - Monitor effectiveness of gowning and training of personnel in aseptic areas
  - Provide information for trending and to identify excursions from normal operating parameters
  - Verify that we continue to maintain an environmentally controlled system as initially established in the validation of the clean room

Environmental Monitoring

- Agar:
  - Jelly-type material
  - Nutrients added to support microbiological growth



Environmental Monitoring

- Airborne Viables are measured:
  - Volumetric (i.e. cfu/m^3)
  - Settling plate (i.e. measured in cfu per unit time collected)
    - 1 cfu/4 hr. period, for a 90 mm settling plate, is requirement for a Grade A room).

Environmental Monitoring

- Airborne Viables
  - Volumetric sampling typically done by sampling a specific volume of air per unit time.
  - Slit to Agar (STA) sampler typically used

Environmental Monitoring

- Airborne Viable- Settling plate
  - Petri dish left in room for a specific period of time.
  - Can correlate number of micro-organisms deposited onto the settling plate to # particles deposited onto an open product container
    - Proportional areas.

Environmental Monitoring

- **Surface Viables**: Measured in cfu per contact plate.
  - Contact Plates often used: RODAC (Replicate Organisms Detection and Counting)
  - Agar is pushed onto the clean room surface to be sampled
  - Then incubate to obtain count per plate

Environmental Monitoring

Other methods of surface sampling including uneven surfaces:

- Cotton Swabs
  - Rub surface to be sampled, then pass over an agar plate.
  - Plate then incubated and counted
- Contact Strips & Slides
  - Strips are removed from containers
  - Applied to the surface to be sampled
  - Incubate, then count

Environmental Monitoring

Sampling Personnel

- Sample gloves – Fingers tips pressed against an agar plate
- Garments/gowns: Press plate or contact strip against the clothing. Best done as they exit the clean room.
  - Could sample at various locations on the body
- Initial qualification sampling more in-depth than routine sampling

EM & FDA Expectations

- FDA expects firms to have a thorough Environmental Monitoring program
  - For critical areas, clear action and alert limits must be specified
  - SOP's must establish frequency of sampling, and type of sampling to be performed, for each type of clean room
  - Trending must be performed
  - Deviations from normal results must be documented on an investigation report
  - Excursions must be explained
  - Corrective action must be taken if applicable

Environmental Monitoring

Environmental Control vs. Monitoring

Environmental Control

Steps taken in the facility/clean room design construction, operation, personnel behaviors, and cleaning and sanitization to limit the presence of micro-organisms in the clean room environment.

Environmental Control Requires:

- Providing/maintaining:
  - Appropriate sterile air flow and air changes
  - Effective sanitization and disinfection
  - Appropriate controls of temperature and relative humidity (RH)
  - Equipment cleaning and sterilizing
    - Especially important
  - Appropriate training and re-training of operators/personnel

Environmental Monitoring

Environmental Control vs. Monitoring

Environmental Monitoring:

Routine microbiological monitoring program that provides a series of snapshots of the microbiological profile of a controlled environment. Routine monitoring ensures that systems continue to provide an environment of consistent quality.

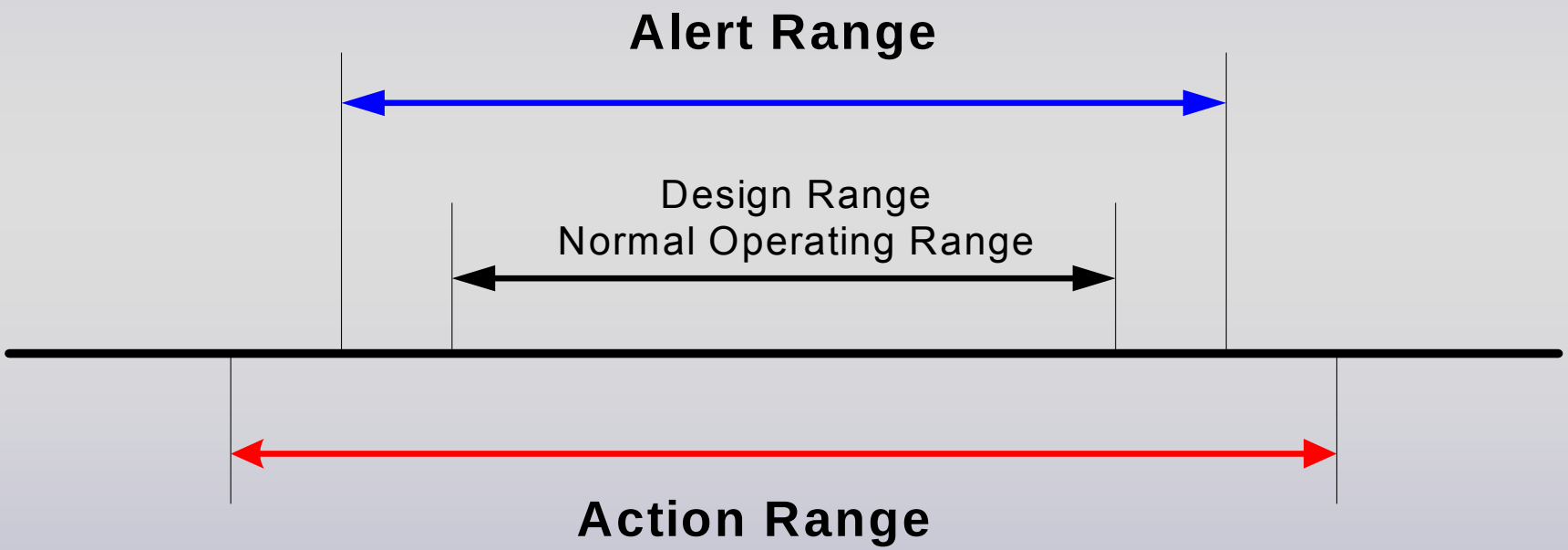
“Alert” Level

- Warning of a potential problem
- Exceeding the alert level signals a potential drift from normal operating conditions
  - Should define the alert level based on history
  - Excursions may or may not require action, but they do require that the situation be closely monitored
  - Frequent alert level excursions will require action

“Action” Level

- Exceeding the action level signals a drift from normal operating conditions
  - Excursions beyond the action level will require some type of investigation and/or **action**
  - The investigation will result in some sort of **action**
  - The action will depend on the frequency of the excursion, the usage of the room, the activity in the room, etc.

“Alert” and “Action” Levels



From Notes # 7

Design Process: Heating Load

- **Types of Heat Loss:**
  - Conduction: (transmission) Heat transfer thru solid surfaces such as walls, floors, roofs.
  - Convection (ventilation) Warm molecules move from one place to another typically by air to air exchange of energy
    - Outside air entering (Doors, fans, etc.)
    - Infiltration leakage through the building envelope is also a convective heat loss
  - Radiation (typically electromagnetic) does not play a large role in calculating the heating load as it is generally a very small amount

Design Process: Heating Load

- Conduction Heat Loss:
  - Conduction: **$Hc = UA(\Delta T)$**
  - U= overall heat transfer coefficient, (btu/hr x area x deg F)
    - $U = \sum (1/R)$
    - R= resistance of the building material
      - R = R1 + R2 + R3
  - A = surface area, in square feet
  - Δ T= temperature difference

Design Process: Heating Load

- Convection Heat Loss:
  - Convection: **Hv=1.08x cfm x (ΔT)**
  - 1.08 = Air factor
  - CFM = Rate air enters the building
  - ΔT= Temperature difference
- Sources:
  - Infiltration: outside air entering though cracks in the building envelope.
  - Ventilation

Design Process: Heating Load

- **Total Heat Loss:**
  - **Ht = Hc + Hv**

Design Process: Cooling Load

- Cooling load is the energy that must be removed to counteract the heat gain.
  - Heat gain components:
    - Conduction heat gain
    - Convection heat gain
    - Solar heat gain
    - Internal heat gain (e.g. lights, motors, equipment)
    - People
  - Cooling load is measured in Btu/hr, or in tons
    - 1 Ton = 12,000 Btu/hr
      - 1 Btu = amount of energy required to raise the temperature of one pound of water 1 degree Fahrenheit.

Design Process: Cooling Load

- Conduction heat gain:
  - **Hc = UA(CLTD)**
  - U= overall heat transfer coefficient
  - A = surface area, in square feet
  - CLTD= cooling load temperature difference
    - Calculated similar to conduction heat loss
    - Recognizes that the exterior temperature of some building materials may exceed the outside temperature. (e.g. tar and gravel roof temperature may exceed 250 deg F during peak outside air conditions).

Design Process: Cooling Load

Convection Heat Gain: (Two (2) parts)

- Sensible Heat Gain
  - **$H_{sens} = 1.08 \times cfm \times (\Delta T)$**
    - *1.08* is called the “air factor”.
      - Air factor units: btu/hr/(cfm) deg F
- Latent heat gain (Moisture load)
  - **$H_{latent} = 4840\ cfm\ (\Delta W)$**
    - W= heat gain from moisture generated in the space
    - Measured in lb of water per lb of dry air

Design Process: Cooling Load

- Internal Heat Gain:
  - From equipment, lights, motors, computers, copy machines
  - Generally adds sensible heat
    - On some occasion, can have equipment that generates a latent load (e.g. vial washing machine).

Design Process: Cooling Load

- Heat Gain from People (Two parts)
  - Sensible Heat Gain
  - Latent Heat Gain
- Hp = People Heat Gain (btu/hr)
  - $Hp = N \times P_s\ (CLF) + N \times P_L$
    - N= Number of occupants
    - P_s=Sensible Heat Gain per person
    - CLF= Cooling load factor; usually 1.0
      - Dependent on number of hours in the space
    - P_L=Latent Heat Gain per person

Calculating the Cooling Load Across a Coil

$$Q_T = 4.5 \times CFM \times \Delta h$$

- Where $\Delta h = h_m - h_o$ (enthalpy of air entering the coil minus enthalpy of air leaving the coil in btu/lb)
  - h_m Enthalpy of mixed air entering the cooling coil in btu/lb
  - h_o Enthalpy of air leaving the cooling coil in btu/lb
- Q_T in btu/hr

Sensible Cooling Load Calculation

- **Qs = AF x CFM x ΔT (AF = air factor) (Equal to 1.08)**

$$Qs = 1.08\ (CFM)\ \Delta T$$

- **ΔT = Temperature difference of air side in degrees Fahrenheit**
- **Qs in Btu/hr**

Latent Cooling Load Calculation

- $Q_L = 4840 \times CFM (\Delta W)$
- ΔW = moisture difference (moisture level entering coil in lb of water / lb of dry air, minus moisture level of air leaving the coil) in lb of water / lb of dry air
- Q_L in Btu / hr

Latent Cooling Load Calculation

- ***If moisture level is given in grains of water per lb of dry air:***
  - **Latent cooling load calculation**

$$Q_L = 0.69 \text{ CFM } \Delta W$$

or

$$Q_L = 0.69 \text{ CFM } \Delta \text{Grains}$$

- **ΔW = moisture difference (moisture level entering coil in grains of water / lb of dry air, minus moisture level of air leaving the coil) in grains of / lb of dry air**
- **Q_L in Btu / hr**
- **Typically use *grains of moisture per lb of dry air***
  - ***Note: 7,000 grains per lb…(4,840 / 7,000 = 0.69)***

Psychrometric Chart Discussion

- Psychrometric chart
- Chart that displays the properties of air and water vapor
- Essential tool for designing temperature and humidity control systems

Enthalpy

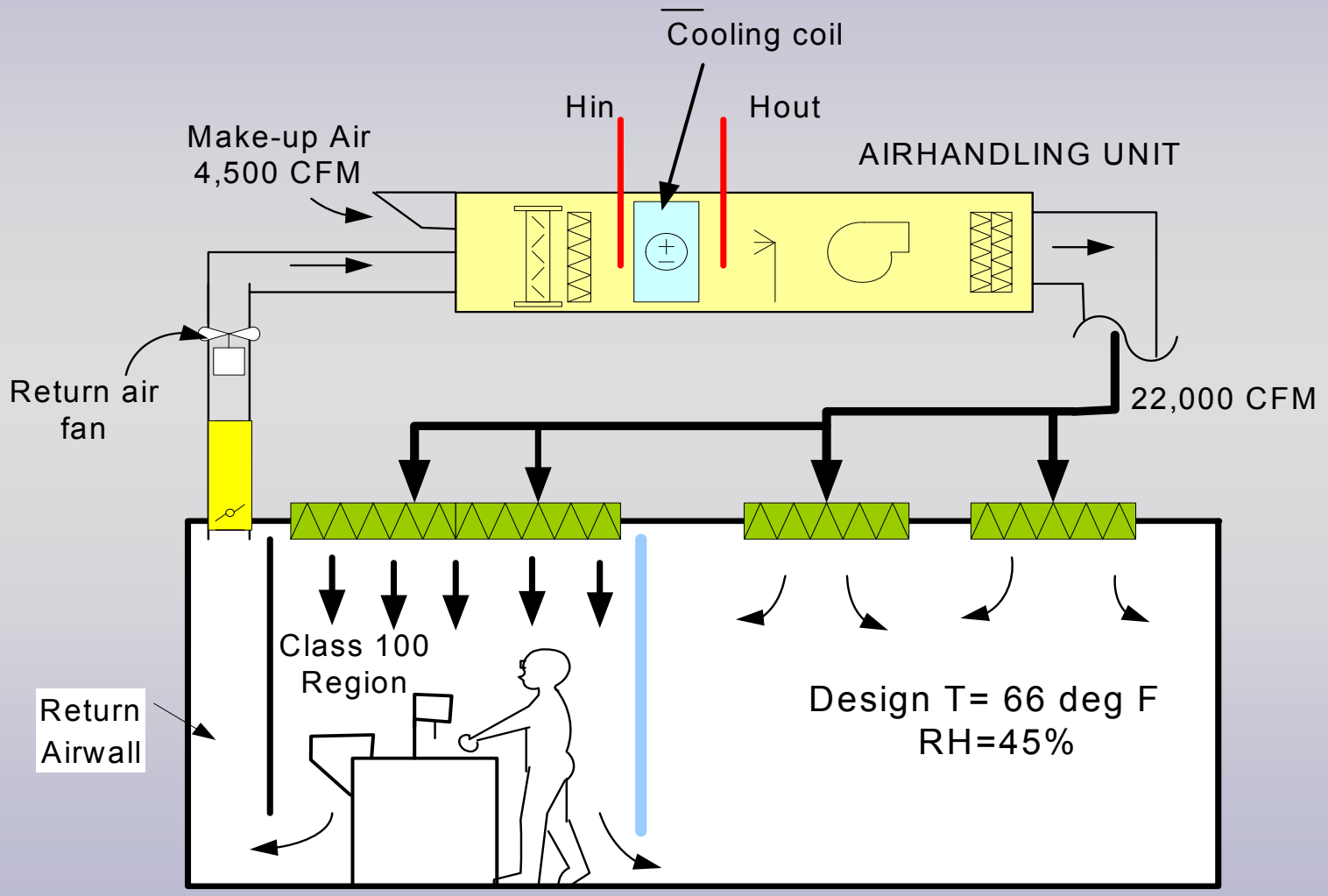
- Total energy in the air
- The higher the sensible temperature, the higher the enthalpy of the air.
- The higher the moisture content of the air, the higher the enthalpy.
- Measured in Btu/lb

Sample problem:
Solve using Psychrometric Chart

Background Data:

- Assume we wish to design an air handling system to serve a sterile fill room. Room design conditions are 66 deg F DB, 45% RH. Assume a design outside air condition of 88 DB, 77 WB. The air handler serving the room supplies 22,000 CFM. Make-up air for pressurization and ventilation is 4,500 CFM. Assume that the exfiltration from the space is equal to the pressurization air of 4,500 CFM, with the balance returning to the air handler. Assume zero duct leakage. Due to the heat gain across the supply fan and supply ductwork, there is a 6 degree rise in supply air temperature. Due to the extensive amount of duct pressure losses, a return fan is installed to boost the pressure in the return duct, to ensure a consistent flow through the air handler. The return fan and return ductwork add 3.5 degrees to the air returning to the air handler. Assume the heat gain in the space is strictly sensible (negligible moisture gain).

Sample problem:



Sample problem:

Based on the information provided,

answer the following:

a) What is the Dry-bulb temperature and wet-bulb temperature of the air entering the cooling coil?

b) What is the cooling load across the coil?

From Notes # 8

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

- **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

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

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:

- 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

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

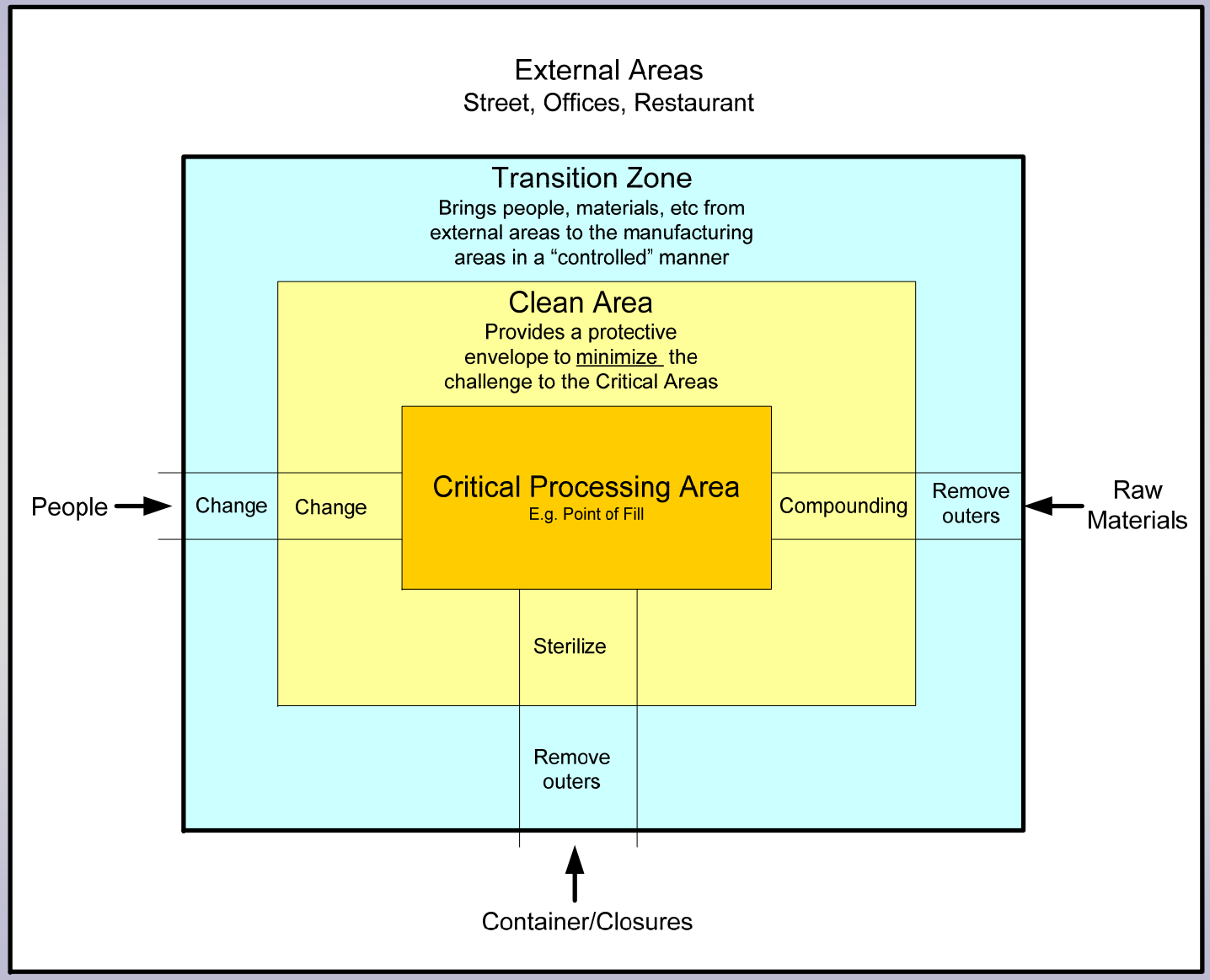
- Concealed, sealed sprinklers should be used to avoid communication between cleanroom and interstitial space
- Electrical outlets should be covered/sealed suitable for washdown service
- Predetermined routes for removing/installing tanks and other stationary equipment
  - Removable wall panels often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

Materials of Construction & Surface Finishes

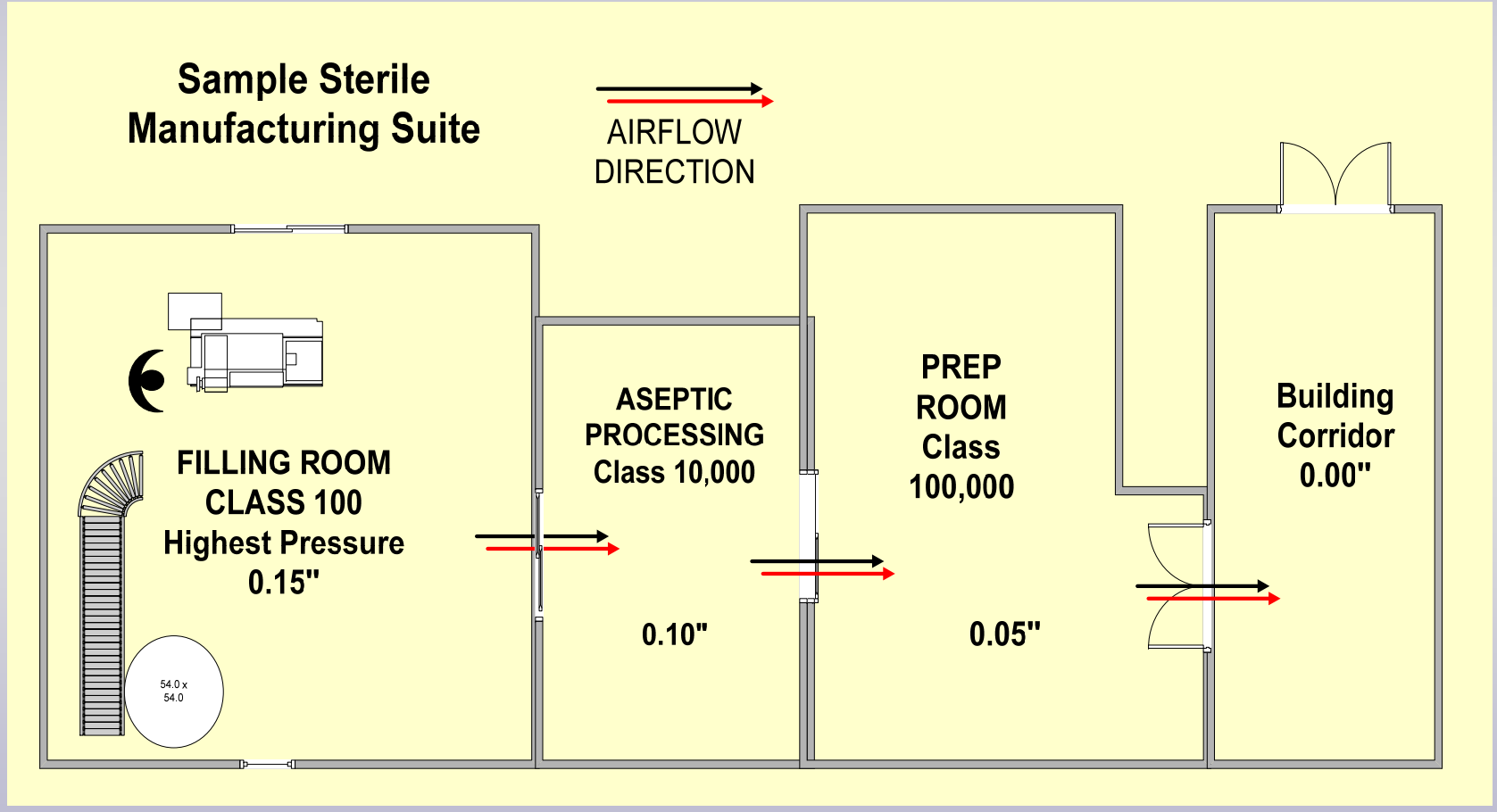
- Platforms typically stainless steel, including decking, stairs and support structure
- Stainless steel screens on HEPA filters
- Stainless steel benchs for gowning areas
- Recessed fire extinguishers with stainless steel frame
- All access panels stainless steel

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
Street, 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

Clean Room Pressurization - Example



From Notes # 9

Primary & Secondary HVAC units

- Primary air handling unit arrangement:
  - One unit is responsible for all of the airflow in the space.
- Primary-Secondary air handling arrangement:
  - Secondary units provide for majority of airflow.
  - Size of primary air handler is reduced.

Air Handling System Arrangement

- Primary air handler provides necessary cooling and heating of air
- Recirculating air handling units near the clean room provide for the necessary airflow
- For Class 100,000 and 10,000 spaces, typically a single unit is used.
- For Class 100 areas, usually use a primary-secondary air handling arrangement.

Other concerns…..

Other factors that can affect unidirectional flow clean rooms

- Thermal currents:
  - Thermal airflows can act against unidirectional flows (e.g. glassware oven after hot glass is unloaded)
- Airflow shading:
  - Dead zone created by obstacle in the way of the unidirectional flow pattern

Regarding returns from clean rooms:

For Class 100,000:

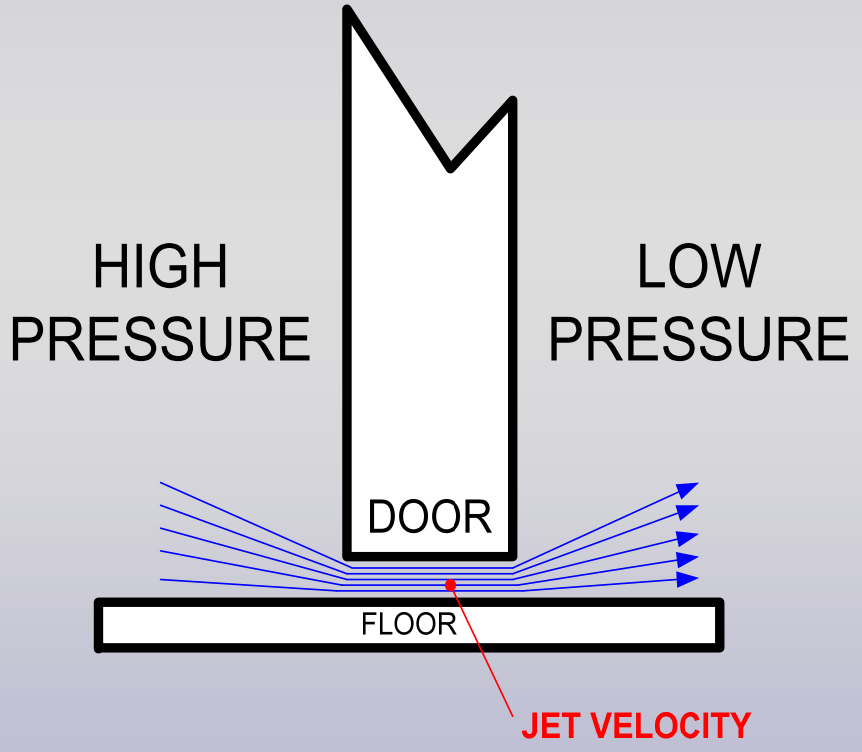
- Ceiling returns are typically used.

For Class 100 and Class 10,000:

- Low return walls are used.

How does pressurization control the movement of particles?

- The jet velocity protects the space, not the pressure!!
- Pressure, is a measure of jet velocity
- Pressure and velocity are inter-related



What Factors Affect Ability to Pressurize

- How porous the room is; how large or small the “crack area” is
  - Space around door frames
  - Lights
  - Piping penetrations
  - Ceiling tiles
  - Windows
- What volume of pressurizing air is available; not all air is “pressurizing air”
- Habits of staff; do they keep doors closed
- Maintenance of equipment

Pressure Levels

- Units of measure
  - IP- inches of water column (visualize)
  - Metric- Pascals PA
- Typical Pressure Levels
  - Class 1 or Class 10 Semiconductor clean rooms; greater than 0.25”wc
  - Pharmaceutical: -0.1 to +0.25; typically 0.05 or 0.03 increments between spaces
  - Laboratories, animal spaces, and isolation rooms; 0.01 to 0.005 inches, space to corridor

Control Terms

- Input Devices
- Output Devices
- Controllers
- Open Loop Control
- Closed Loop Control
- On/Off Control
- Continuous Control
- Control Terms
  - Gain
  - PID (Proportional, Integral, Derivative)

From Notes # 10

Calculating required CFM for cooling a space

When sensible load, supply air temperature and room temperature are known

$$CFM = \frac{Q_s}{1.08 \triangle T}$$

Where $\Delta T = T_{rm} - T_{sa}$ = Temperature difference between room and supply air from air handler

Calculating required CFM to the space

If supply air temperature is known:

First find the required supply air temperature needed to meet the required internal sensible and latent heat gains

1. **Plot room space conditions**
2. **Calculate SHR**
3. **Draw a line from the SHR mark through the standard space condition point ("SHR line")**
4. **Draw a line that goes through the room space condition which is parallel to the "SHR line"**
5. **Read the temperature where this line meets the saturation line**
   - ⇨ **This is the best supply air temperature that would simultaneously satisfy the sensible and latent heat gains in the space.**
6. **Solve for CFM by using:** $$CFM = \frac{Q_s}{1.08\ \triangle T}$$

Pyschrometric Sample Problem

A pharmaceutical company wishes to construct a manufacturing space which will require an HVAC system that functions within the following parameters:

- Space drybulb temperature = 70°F
- Space relative humidity = 50%
- Internal sensible load (Q_s) = 88,000 BTU/hour
- Internal latent load (Q_L) = 12,000 BTU/hour
- Minimum outside air flow = 400 CFM
- Design outdoor air drybuib temperature = 94°F
- Design outdoor air wetbulb temperature = 74°F

Problem

- 1. Calculate the required supply airflow and temperature
- 2. Calculate the cooling coil load to provide this supply air using mixed air
- 3. Calculate the cooling coil load to provide this supply air using 100% outside air

HVAC System Components

- Air handling unit
- Ductwork
- Dampers
- Duct-mounted heating coils
  - “Reheat coils”
- Airflow stations
- Duct-mounted humidifiers

HVAC System Components

- Instruments and controls
- Diffusers
- Exhaust fans
- Return air fans - Inline with duct
- Secondary recirculating fan systems
- Smoke detectors

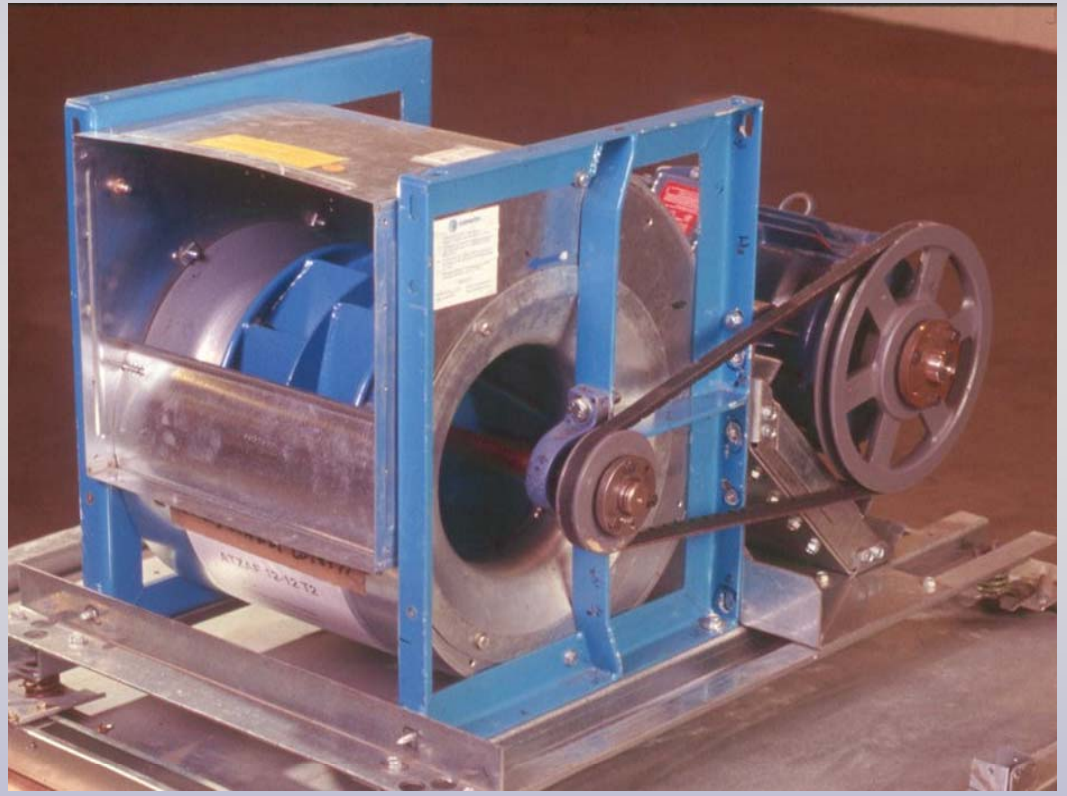
HVAC System

Air Handling Unit:

- **Fans to deliver the air. Some have a return fan as well as a supply fan**
- **Filter sections to filter the air**
- **Contains heating and cooling coils to heat or cool the air**
- **Cooling coil also dehumidifies since it removes moisture from the air**
- **Heating coil at unit preheats the air to prevent freezing downstream components, such as cooling coil**
- **Dampers which control the amount of air brought in from outside or from the return air stream, or to adjust the amount of air that is directed toward the cooling coil**
- **Mixing box with dampers**

Fans

- **Forward-curved (Housed)**
- **Backward-curved (Housed)**
- **Airfoil blade (Housed)**
- **Airfoil blade (Plenum)**
- **Vane axial Q-Fan (Duct)**



Levels of Filtration (AHU)

Filters:

- Reduce particulate load in the space.
- Protects cooling and heating coils.
- Extends life of HEPA filters in system
- Helps maintain cleanliness of ductwork and systems

Typically two or three levels of filtration at the air handling unit
Initial: Prefilters. 20 -30 %
Intermediate filters: 80 - 90 %

Intermediate filter is typically bag filter type, with efficiency of about 50% against the 0.5 micron particle).

Cooling Coils

- Types:
  - Chilled water
    - Tonnage vs chilled water flow rate
  - Direct expansion
    - Refrigerant in coil

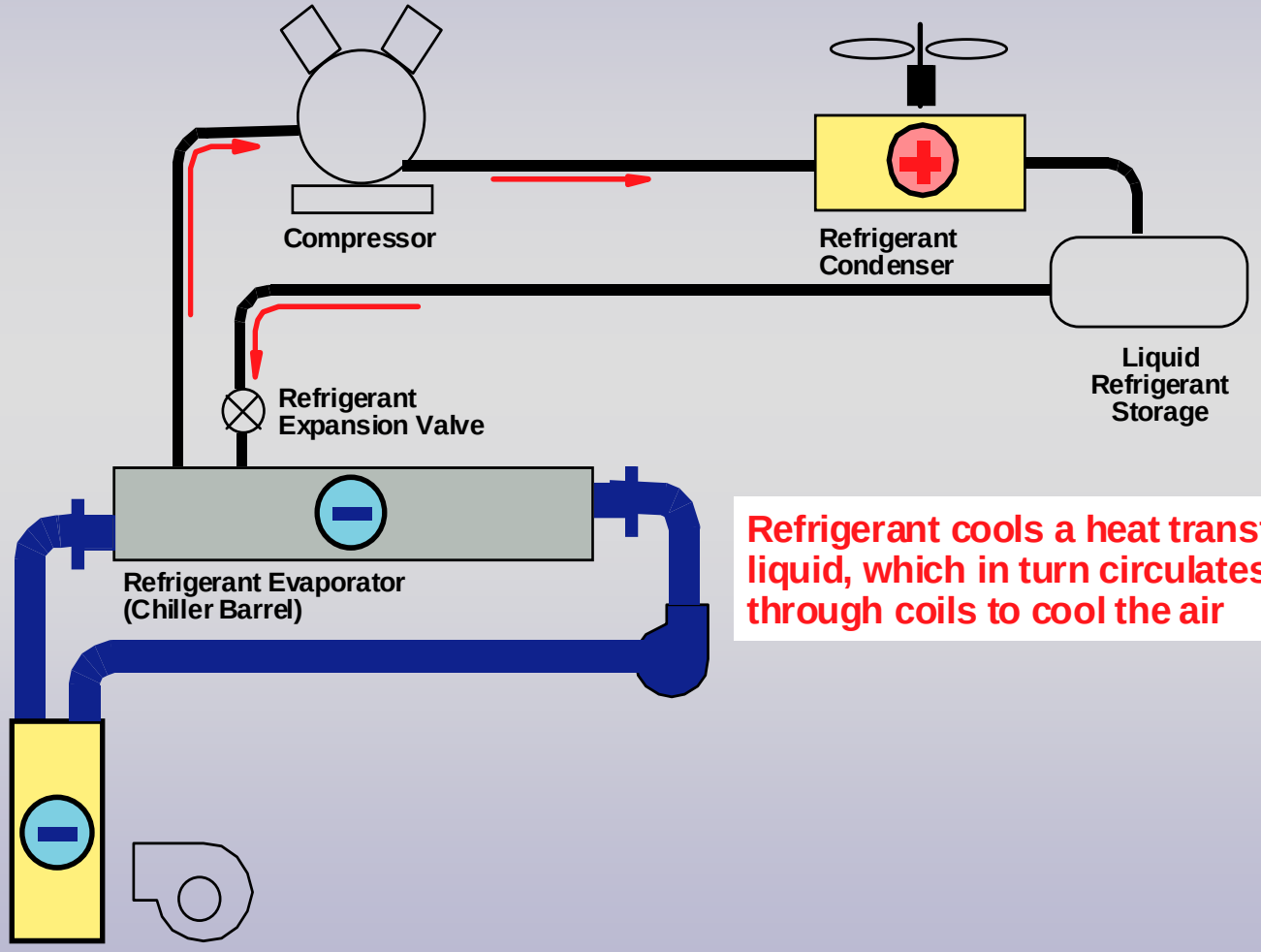
Need for Humidification

- Product requirements
  - hygroscopic materials
- People comfort
- Organism growth control
- Static electricity
- Requirements for GMP compliance
  - Must be “controlled”

Humidifiers

- Types/methods:
  - Steam
    - Industrial steam
    - Pure steam (preferred for pharmaceutical applications
  - Water
    - City water (tap water)
    - Softened water
    - Deionized water
    - Water for Injection

Chilled Water, Glycol & Brine Cooling



Refrigerant cools a heat transfer liquid, which in turn circulates through coils to cool the air

Desiccant Dehumidification

- With cooling-based dehumidification, it is possible to reach 45°F dew point using chilled water, and 40°F dew point using refrigerant (DX) coil.
- Can achieve lower dew points (lower humidity ratios) with desiccant dehumidification than cooling-based dehumidification.
- Theoretically, desiccant dehumidification runs along a constant enthalpy line. In actuality, there is a slight rise in the enthalpy.

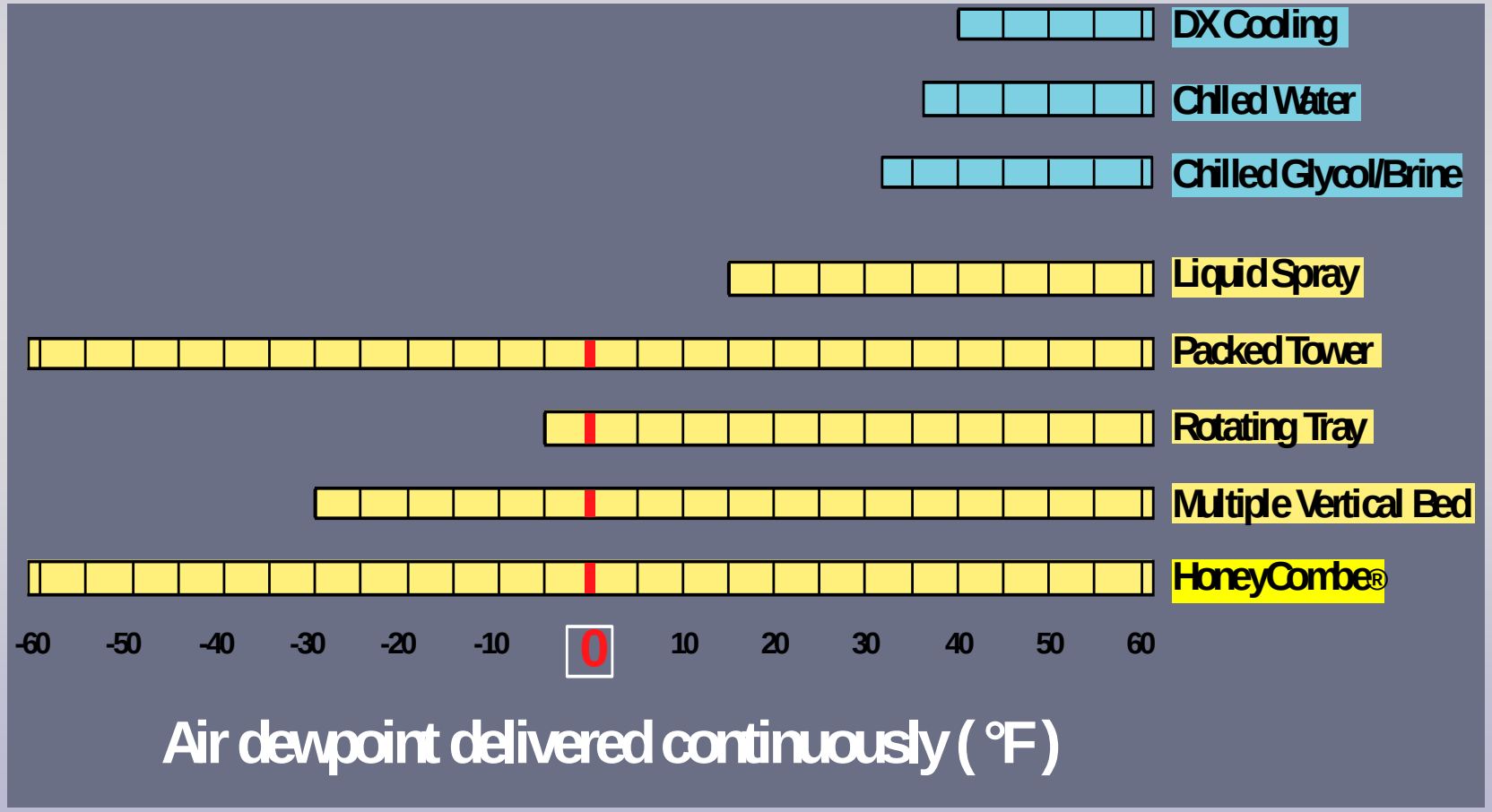
Desiccant Dehumidification

- Moisture leaves the air stream due to difference in vapor pressure
  - Low vapor pressure at surface of desiccant
  - Vapor pressure of water in air is higher than at surface of desiccant
  - Moisture moves from the air stream to the desiccant
  - Most solid materials attract and hold moisture

Desiccant Dehumidification

- Desiccants are unique – they can hold 10-10,000 % their weight in water vapor.
- Desiccant vapor pressure (VP) varies with temperature
- At high temp's, VP is high, and the desiccant gives off vapor
- At low temp's, VP is lower and absorbs moisture
- Vapor moves from air to the desiccant and back again based on vapor pressure differences

Comparing Dehumidifiers By Leaving Air Dew Point



Cooling vs. Desiccant Dehumidifiers

- Most economical when used in combination
- Factors favoring cooling based dehumidification:
  - Low electrical cost (below 5¢/kWH)
  - Humidity control at high temperatures
    - Need for high relative humidity (e.g. fruit)

Humidity Control Advantages

- Corrosion Prevention
- Condensation Prevention
- Mold & Fungus Prevention
- Moisture Regain Prevention
- Product Drying
- Dry Cooling
- Food Processing
- Pharmaceutical Processing

Pharmaceutical Processing

- **Tableting Presses**
  - Eliminates moisture regain
  - Allows faster press speed
  - Allows constant production rate
- **Lyophilizer Rooms**
  - Prevents moisture regain
  - Avoids need for glove boxes
  - Improves shelf life
- **Spray Drying**
  - Consistent production
  - Reduced size of fluid bed
  - Allows low-temp drying
- **Tablet Coating**
  - Allows reduction of solvents
  - Consistent drying in all climates & seasons
- **Powder Compounding**
  - Eliminates moisture regain
  - Simplifies handling
  - Improves sanitation
- **Storage**
  - Allows low rh in cold storage
  - Prevents cardboard regain
  - Extends storage life

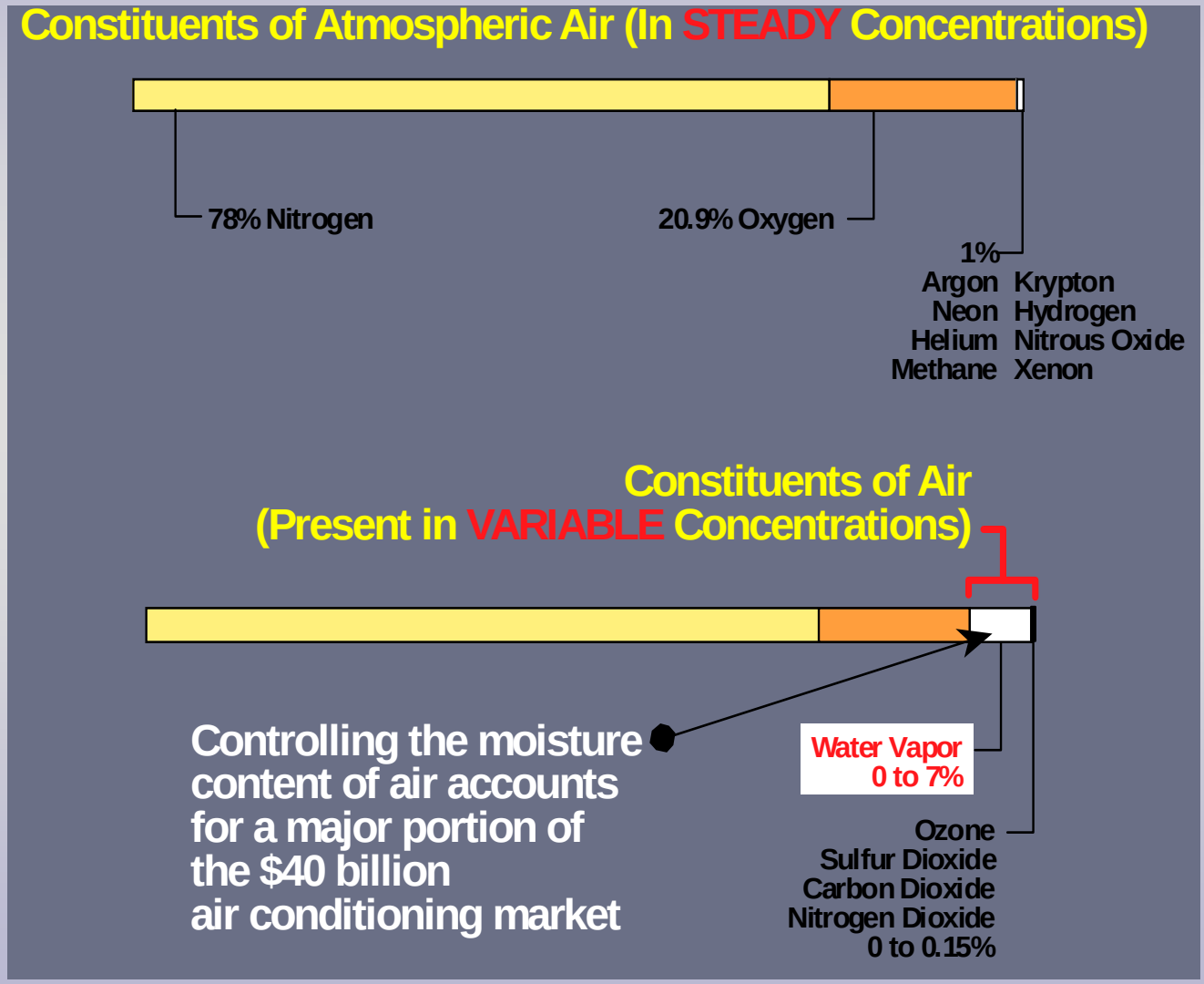
Moisture Load Sources

- Internal Loads
  - Vapor Permeation through walls, floor & ceiling
  - Evaporation and respiration from people
  - Desorption from moist products
  - Evaporation from wet surfaces
  - Vapor as a product of combustion
  - Humid air infiltration through cracks, holes & door openings
- External Loads
  - Vapor carried into the system by moist ventilation air

Typical Air Leak Paths

- Air Handling System
  - Air duct joints
  - Access panels in air handling equipment
  - Ventilation louvers in doors
  - Unused exhaust fans and back-draft dampers
  - Window air conditioners
- Room Construction
  - Wall-to-ceiling, wall-to-floor joints
  - Cracks around doors; especially at the floor
  - Open construction above suspended ceiling tiles
  - Wall penetrations for electrical boxes, conduits, pipes & light fixtures
  - Vapor barrier plastic sheets, not joined

The Humidity Variable In Air



Dehumidifier Performance

- How dry is the air after it leaves the dehumidifier? ..... That will depend on:
  - Moisture content of the entering process air
  - Temperature of the entering process air
  - Velocity of the process air through the desiccant
  - Temperature of the entering reactivation air
  - And to a lesser extent:
    - Moisture content of the reactivation air
    - Velocity of the reactivation air through the desiccant
    - Amount of desiccant exposed to the air
      - Wheel rotational speed (eg)
    - Sorption-desorption characteristics of the desiccant

Clean Utilities

- Water Systems
  - Deionized
  - Purified
  - WFI
- Clean/Pure Steam
- Clean-in-place (CIP, SIP, WIP)
- HVAC
- Pure Gasses