Hands-On Workshop

Drug Product Manufacturing: Formulation, Fill, and Finish

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Drug Products

Drug Products for Human and Animal Consumption are regulated by the Food and Drug Administration (FDA), which has very strict guidelines on how these are developed, manufactured, and distributed

Drug Products

The Food, Drug, and Cosmetic Act was enacted in 1938.

The Code of Federal Regulations (CFR) part 210 and 211 cover all aspects of prescription drug products including the current Good Manufacturing Practices (cGMP's)

Drug Products

Document Control

- Drug Master File – Batch Records
- SOP’s
- Validation Records
- Environmental Records
- Stability Records
- Process Logs
- Material Logs
- Distribution Record
- Complaint Files
- Retained Sample Storage Area Records
- Returned Goods Records

Sterile Drug Products

Equipment and Facilities Management

- General Air Conditioning
- Controlled Air
- Sterile Area
- Humidity Controlled Sterile Areas

Drug Products

Facilities Preparation

- Cleaning of Service Areas
- Preparation of Clean Room Areas
- Office Areas

Drug Products

Equipment Preparation

- Clean in Place (CIP)
- Steam in Place (SIP)

Drug Products

Packaging Component Preparation

- Washing
- Sterilization (Autoclave or Oven)
- Siliconization

Packaging Configurations

Sterile Compounding Facilities

Q: What are the major concerns when manufacturing a parenteral dosage form (compared to an oral dosage form)?

Sterile Compounding Facilities

- Sterility
- Pyrogens (Endotoxins)
- Extraneous Particulate Matter
- [Iso-Tonicity]
- [Physiological pH]

Sterile Compounding Facilities

Parenteral Products

- Solutions
- Suspensions
- Emulsions
- Sterile Solids (powder fill and lyo)

Unit Operations for Sterile Manufacturing of Solutions and Freeze Dried Powders

- Component Sterilization
- Compounding
- Mixing
- In-Process Testing
- Filtration
- Filling
- Stoppering
- Freeze Drying
- Sealing
- Terminal Sterilization
- Final Product Testing

Sterile Compounding Facilities

The Sterile Product Manufacturing Plant

Sterile Compounding Facilities

Facilities

GMP requirements

- Section 211.42: Must be separate or defined areas of operation to prevent contamination, and that for aseptic processing there be, as appropriate, an air supply filtered through HEPA filters under positive pressure, and systems for monitoring the environment and maintaining equipment used to control aseptic conditions.

Sterile Compounding Facilities

Facilities

GMP requirements

- Section 211.46: Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature be provided where appropriate and that air filtration systems, including prefilters and particulate matter air filters, be used when appropriate on air supplies to production areas.

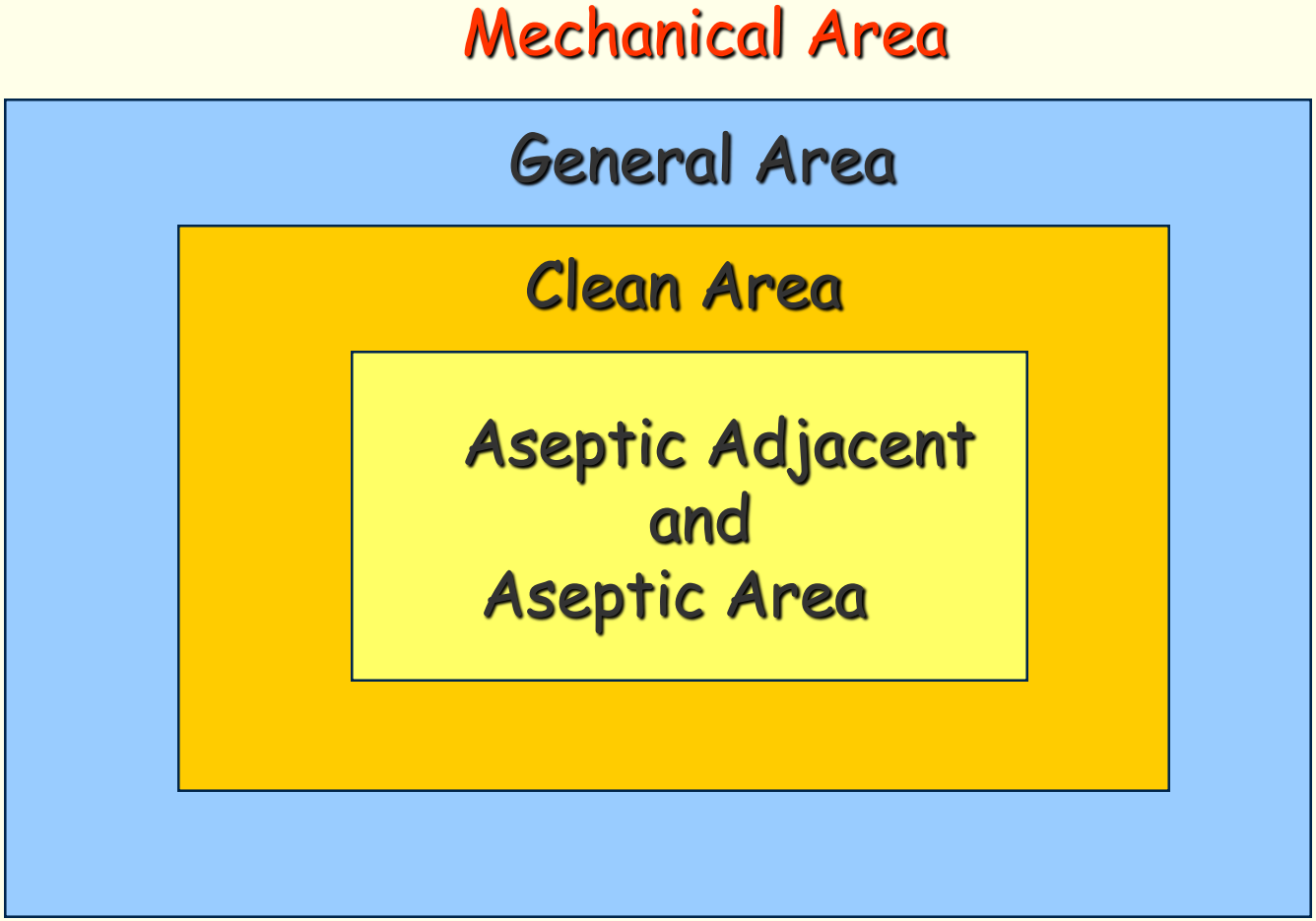
Sterile Compounding Facilities

Facilities

GMP requirements

- Section 212.42 (proposed GMP for LVP)
  - Walls, floors, ceilings, fixtures, and partitions in controlled environment areas shall
    - Have a smooth, cleanable finish that is impervious to water and to cleaning and sanitizing solutions
    - Be constructed of materials that resist chipping, flaking, oxidizing, or other deterioration.

Sterile Block Design



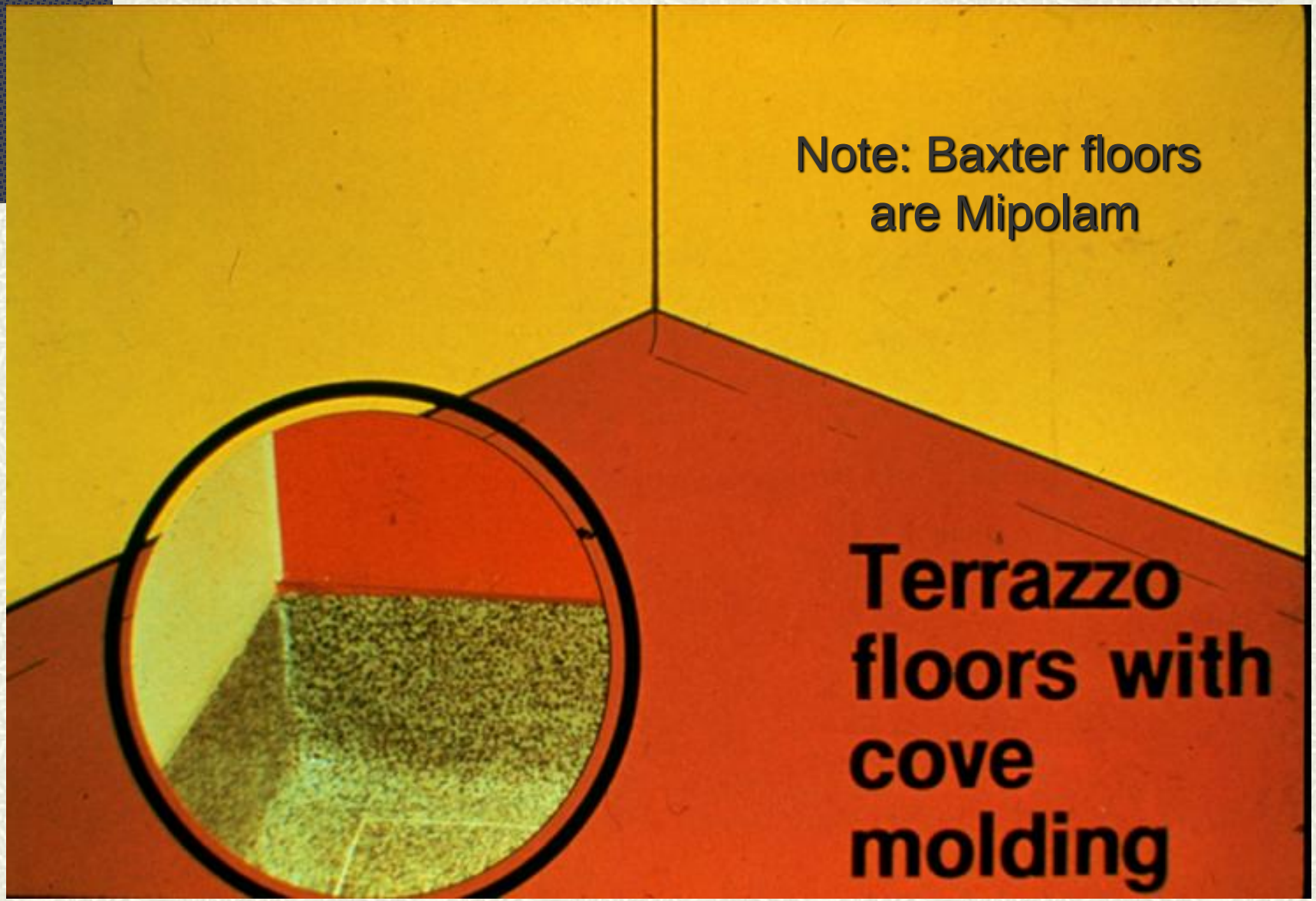
Facility Construction, Design, and Materials for Sterile Products Manufacturing

1. Floors, walls, ceilings, fixtures, partitions in critical areas must have these three characteristics:

   (a) Smooth, hard finishes impervious to water, resistant to deterioration

   (b) Surfaces that are easily cleanable

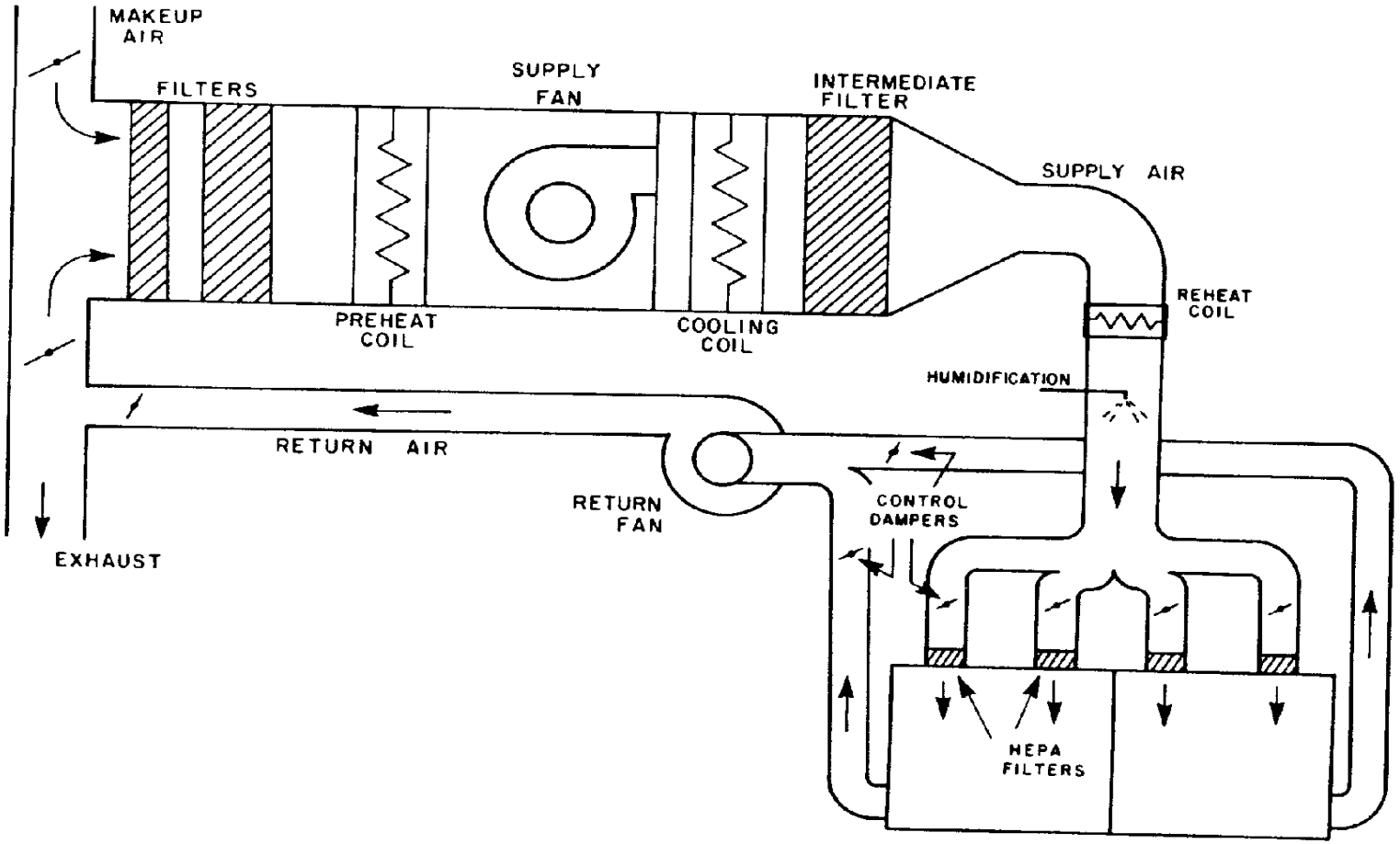
   (c) Continuous surfaces, no sharp corners


Note: Baxter floors
are Mipolam
Terrazzo
floors with
cove
molding

Facility Construction, Design, and Materials for Sterile Products Manufacturing

1. Air supply must be filtered through HEPA filters under positive pressure Room pressure increases as level of cleanliness increases

2. The most critical area is defined as Class 100
   This is where sterile products/materials are exposed to the environment This area can have no drains in the floor


MAKEUP AIR
FILTERS
SUPPLY FAN
INTERMEDIATE FILTER
SUPPLY AIR
REHEAT COIL
PREHEAT COIL
COOLING COIL
HUMIDIFICATION
RETURN AIR
RETURN FAN
CONTROL DAMPERS
EXHAUST
HEPA FILTERS

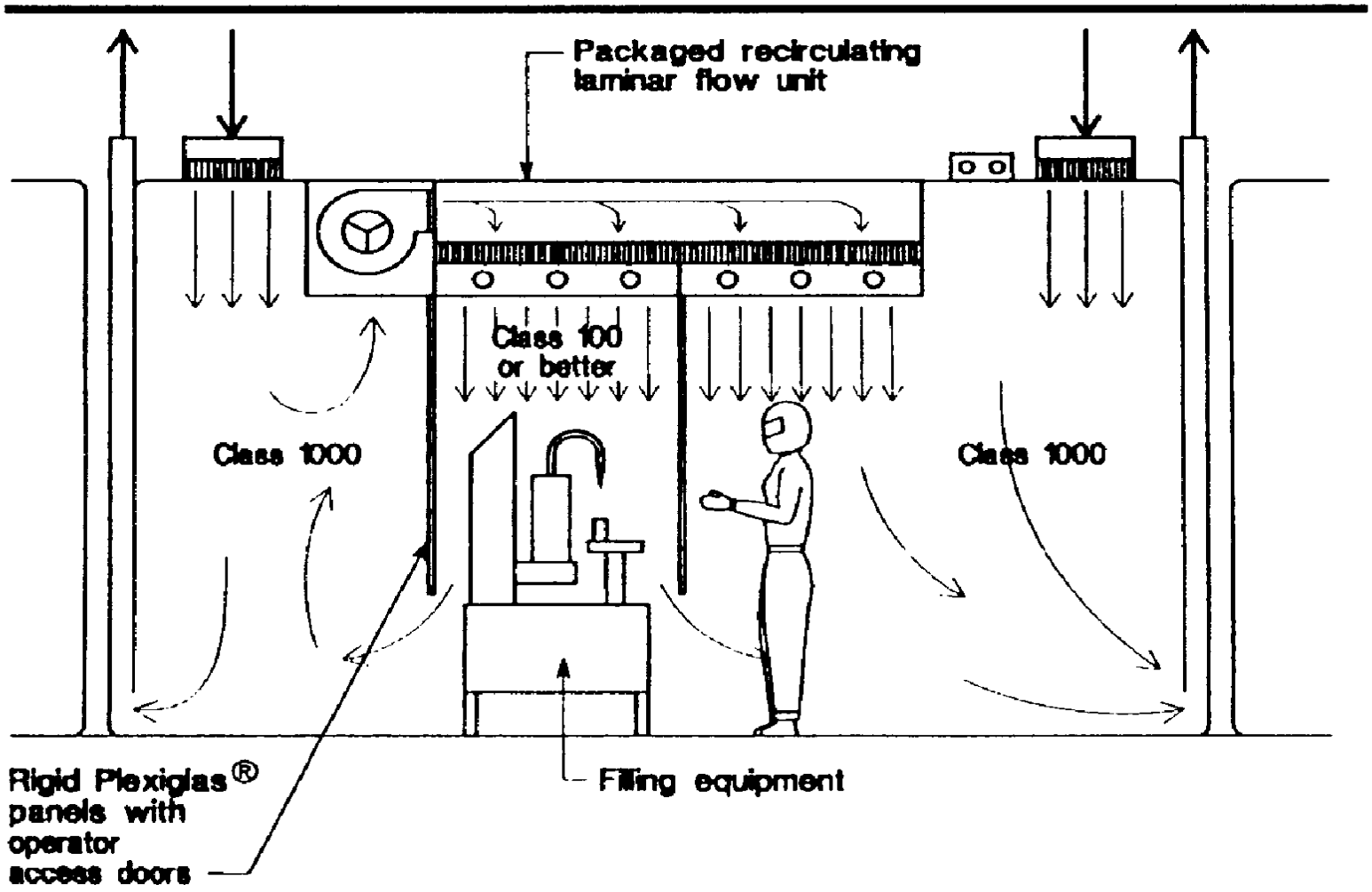


Figure 3.8. Enhancement of filling line with packaged laminar flow unit.

The Problem of People in Sterile Product Processing

- People generate large amounts of particles!
- Each adult loses a complete layer of skin about every 4 days; equivalent to 10,000,000 particles per day.
- Class 100 aseptic conditions allow only 100 particles per cubic foot >0.5µ. Therefore, people in the area are major problems for control of cleanliness

Human Skin Contamination

- > 1.2 million aerobic bacteria per m^2 in head and neck region of both male and female subjects.
- 0.9 – 3 million per m^2 on hands and arms
- Much higher numbers of viable anaerobes (primarily *Proprionibacterium acnes*)

Ljungqvisdt and Reinmueller, Ventilation and Airbone Contamination in Clean Rooms, Tryckeri PriCor, Sweden, 1995

BODY EMISSIONS RELATED TO ACTIVITY*

Type of Movement	Particle Emission/Min. Greater than 0.3 Microns Diameter
Standing or sitting down without movement	100,000
Sitting down with modest movement of head, hand, or lower arm	500,000
Sitting down with moderate movement body, arm and some movement of the feet	1,000,000
Standing up with full body movement	2,000,000
Slow walk (~2.2 mile/hour)	5,000,000
Walking ~3.8 miles/hour	7,500,000
Walking ~5.6 miles/hour	10,000,000
Violent exercise	15,000,000 to 30,000,000

* Howorth, "Movement of Airflow, Peripheral Entrainment, and Dispersion of Contaminants", J. Parenteral Sci Tech., 42, 14-19, 1988

Sterile Compounding Facilities

Water Systems

Water used in parenteral manufacturing must be classified as Water for Injection (WFI)

Meets Requirements for:

- Endotoxin
- Total Organic Carbon
- Conductivity

Sterile Compounding Facilities

WFI Water Systems

The following steps are used to produce WFI:

- Carbon Bed Filtration (Removal of organics)
- Water Softening (Removal of $CaCO_3$ and other minerals
- Steam sterilization or reverse osmosis
- Stored in 316 stainless steel tank

Sterile Compounding Facilities

WFI Water Systems

Electro-polished 316 stainless steel required

WFI recirculated at 80°C to prevent growth of microorganisms

System regularly monitored for levels of endotoxin and microorganisms

Depyrogenation

- **Elimination or removal of pyrogens which are metabolic by-products of microbial growth**
  - **Water is main source**
- **Pyrogens also called Endotoxins**
  - **Death from sepsis actually due to effects of endotoxin contamination rather than the microbial contamination**
- **Pyrogens are non-living liposaccharides so you cannot kill them, only destroy or remove.**
- **Pyrogens very small, can pass through sterilizing membranes**

Sterile Compounding Facilities

Formulation

- Formulation typically in Class 100,000 area
- Excipients/Active brought together with WFI in a 316 stainless steel (or glass) vessel
- All excipients/active must be tested and released prior to use.

Sterile Compounding Facilities

Filtration and Filling

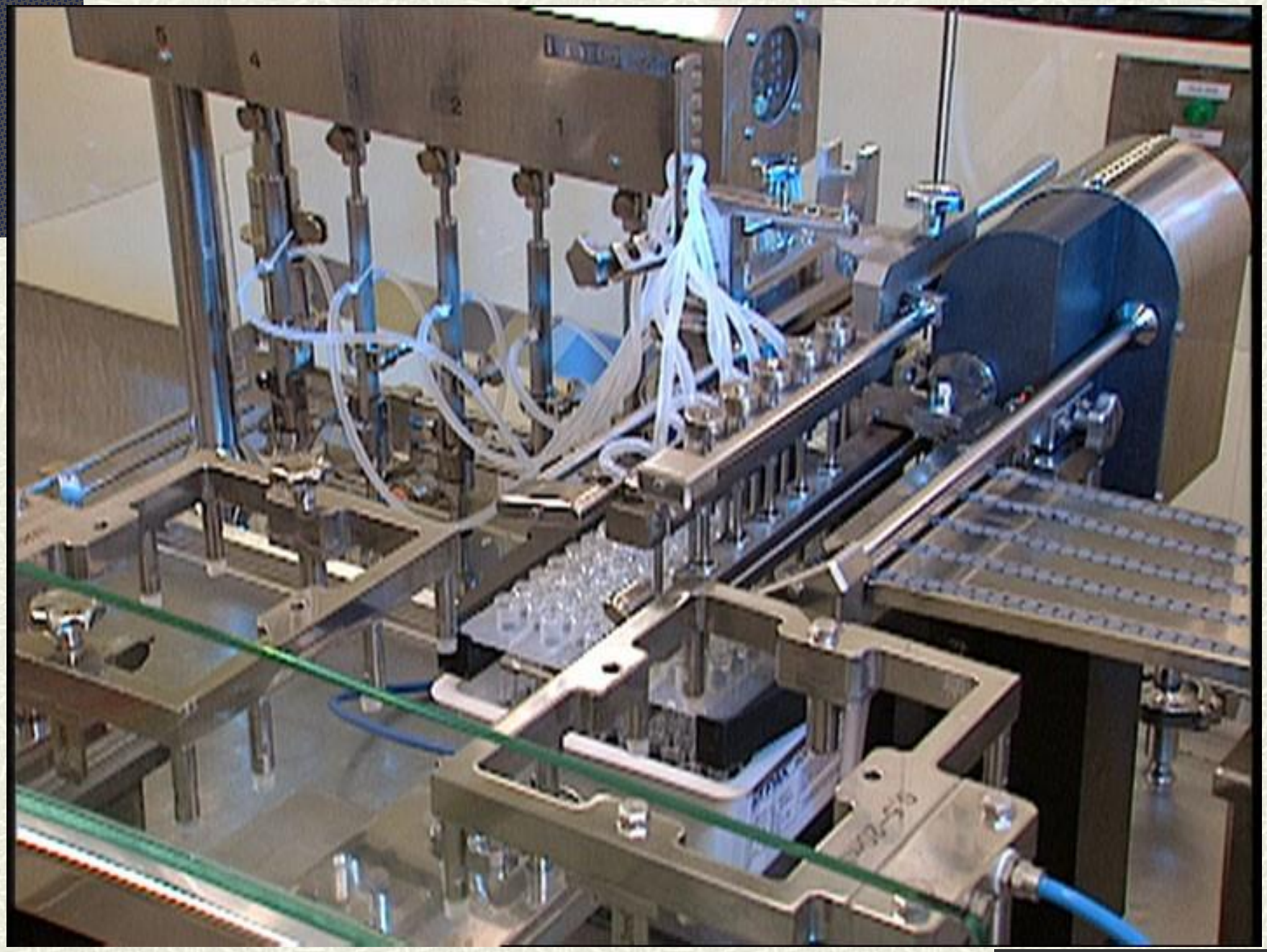
- Formulation pumped through portal into class 1000 filling suite and sterile filtered (0.2 µm Filter)
- Formulation pumped to filling line (Class 100) and fill volume adjusted via weight shots

Sterile Compounding Facilities

Aseptic Processing vs. Terminal Sterilization

Aseptic Processing: Formulation and container closer individually sterilized and brought together in a sterile environment.

Terminal Sterilization: Formulation and container closer individually sterilized and brought together in a sterile environment. Finished product is sterilized usually via steam. (Required if product can withstand process)



Environmental Monitoring Methods

AIR

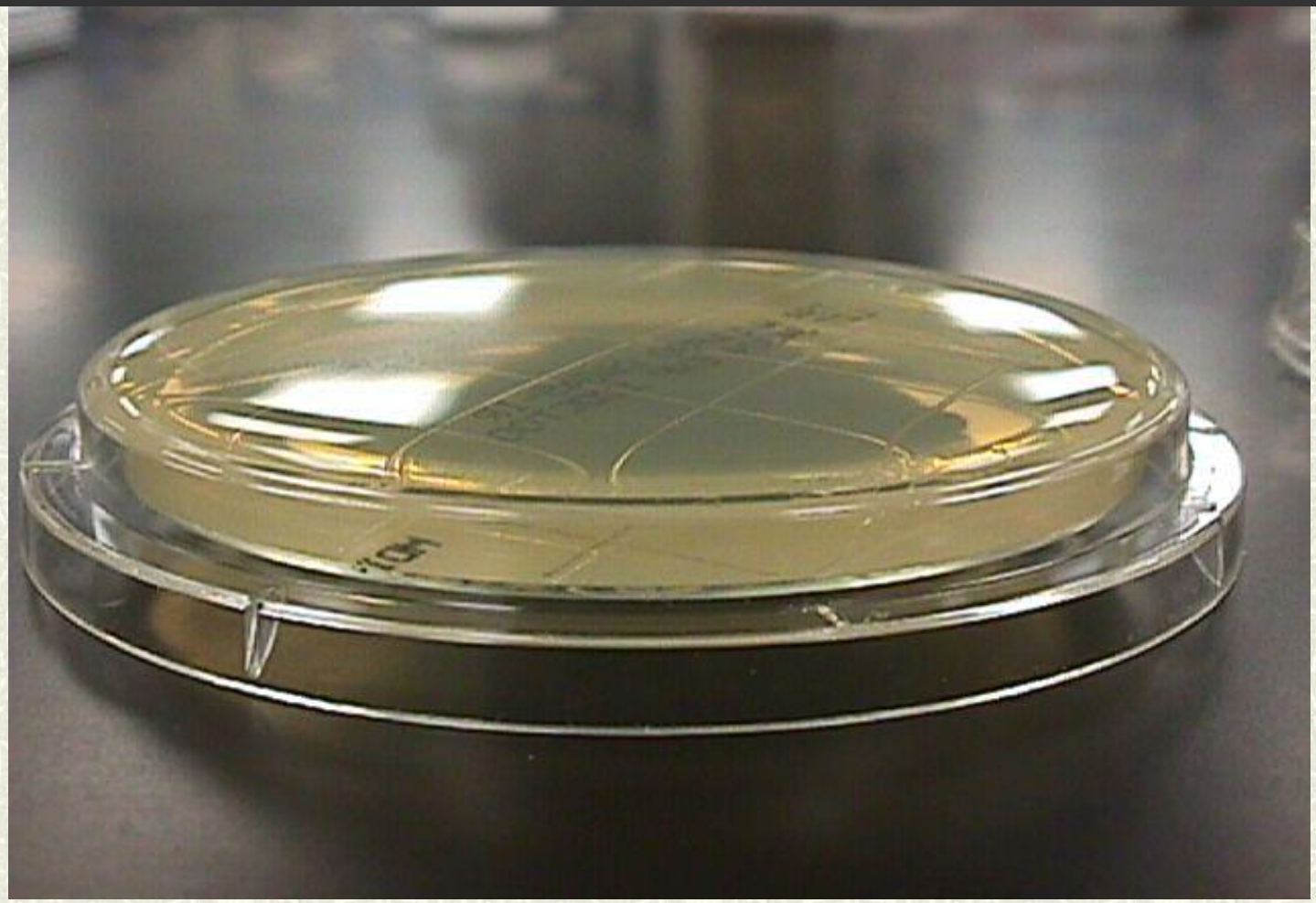
- Viable Particles
  - Nutrient agar plates
  - Slit samplers
- All Particles
  - Electronic counters

SURFACE

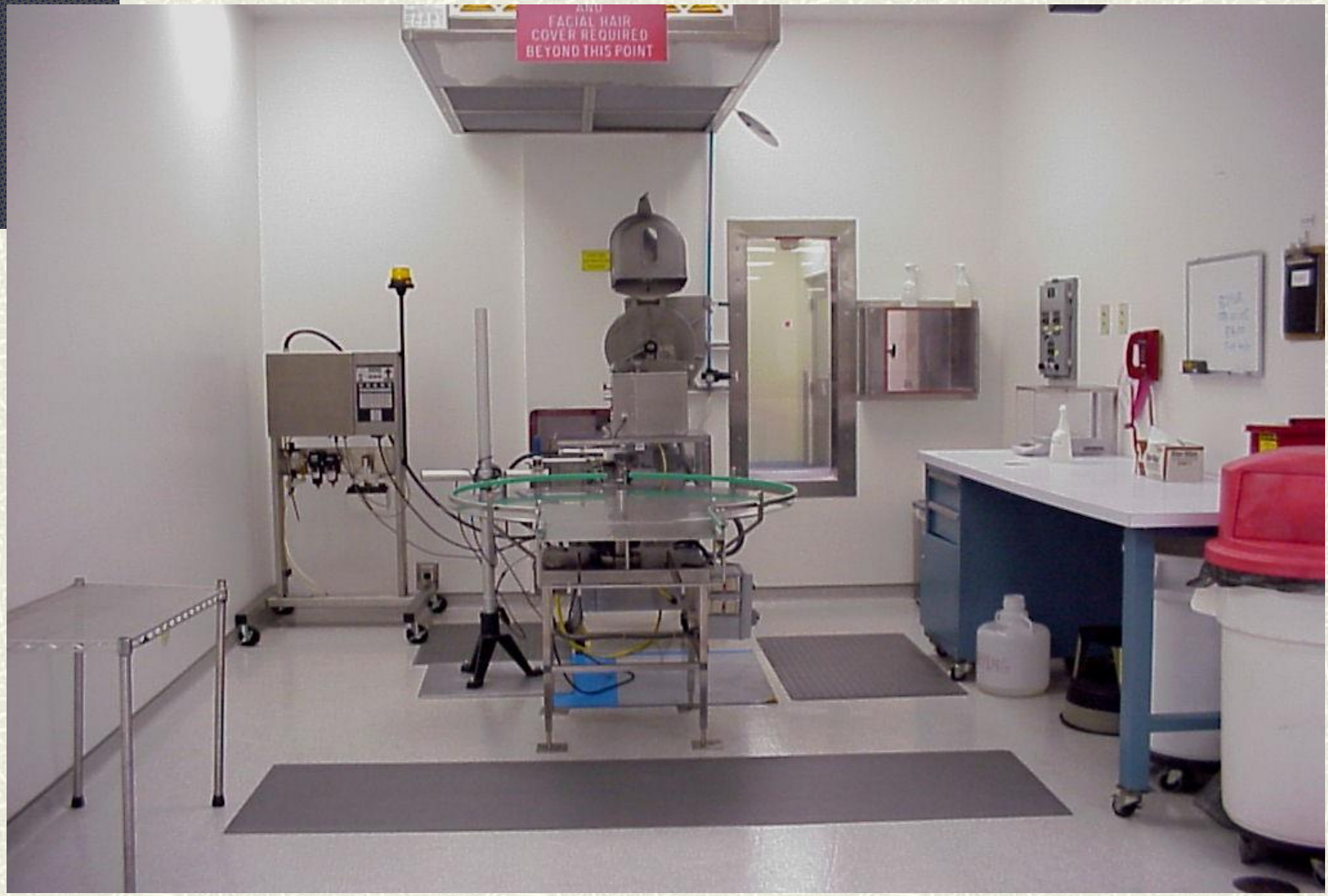
- Viable Particles
  - Rodac plates
  - Swab rinse
- Non Viable Particles
  - Garment sampler

Settle Plates & Steritest Cylinders

Rodac Plate



Slit–to-Agar Plate


AND
FACIAL HAIR
COVER REQUIRED
BEYOND THIS POINT

Selecting Formulation Components

- Buffers
- Bulking Agents
- Tonicity Agents
- Stabilizers
- Surfactants
- Solubilizing Agents
- Antioxidants
- Chelating Agents
- Preservatives

Accelerated Stability

Drug products have a fixed shelf life, which is dependent on a number of things:

- Temperature
- Light
- Oxygen
- Water

Accelerated Stability

Trying to Predict Shelf Life is Critical in Formulation Development Screening

Placing samples at elevated temperatures speeds up the degradation mechanisms allowing the determination of the optimal formulation

Accelerated Stability

- Drugs degrade over time at a specific rate (loss/time) according to the rate laws (Order):

In general, most drugs degrade by 1st order kinetics (exponential decay)

$$\ln[A] = -kt + \ln[\mathrm{A}]_0$$

$$A_t = A_0 e^{-kt}$$

Accelerated Stability

Rate constants (k) are temperature dependent and will be different for each temperature tested (higher temperature = larger rate constant)

The goal of today's exercise is to determine the rate constants at 3 different temperatures for the degradation of aspirin and predict shelf life (10% loss) at 25°C

Accelerated Stability

- The rate constants will be plotted as a function of temperature (K) giving the following equation of a line:

$$\ln(k) = -\frac{E_a}{R}\left(\frac{1}{T}\right) + \ln(A)$$

Accelerated Stability

For Example, if we want to know when our drug (aspirin) is sub-potent (90%) at 25°C, we use the following equation to determine the rate constant:

$$\ln(k) = -\frac{E_a}{R}\left(\frac{1}{T}\right) + \ln(A)$$

Then use: $\ln(0.9) = -k_{25}t$

or: $\frac{0.1054}{k_{25}} = t$