# PhEn-602
# Pharmaceutical Facility Design

## Notes #3
## J. Manfredi

# From the new, soon to be released film: A Few Good Engineers

**CAST: Engineer: Jack Nicholson Architect: Tom Cruise**

- *Engineer:* You want answers?
- *Architect:* I think I'm entitled to them.
- *Engineer:* You want answers?!
- *Architect:* I want the truth!
- *Engineer:* You can't HANDLE the truth!!

  Son, we live in a world that has CHILLERS, BOILERS AND SWITCHGEAR. And those PIECES OF EQUIPMENT have to be LOCATED IN ROOMS. Who's gonna DESIGN THEM? You? You, MR. ARCHITECT? I have a greater responsibility than you can possibly fathom. You weep for LOST PARKING SPACES and you curse the SIZE OF MY GENERATOR. You have that luxury. You have the luxury of not knowing what I know: that THOSE MEP SYSTEMS, while tragic, probably saved lives. And my existence, while grotesque and incomprehensible to you, saves lives...You don't want the truth. Because deep down, in places you don't talk about at parties, You WANT me on that DESIGN TEAM. You NEED me on that DESIGN TEAM. We use words like DESIGN, CODE, ANALYSIS...we use these words as the backbone to a life spent PROVIDING OWNER COMFORT AND ENERGY EFFICIENCY. You use 'em as a punch line at a party.

  I have neither the time nor the inclination to explain my DESIGN to a man who rises and sleeps under the blanket of the very ENVIRONMENT that I provide, then questions the manner in which I provide it! I'd rather you just said thank you and went on your way. Otherwise, I suggest you pick up a DUCTULATOR and DESIGN a BUILDING SYSTEM. Either way, I don't give a darn what you think you're entitled to!
- *Architect* : Did you OVERSIZE THE MECHANICAL AND ELECTRICAL ROOMS?
- *Engineer* : (quietly) I did the job you HIRED me to do.
- *Architect* : Did you OVERSIZE THE MECHANICAL AND ELECTRICAL ROOMS?!!
- *Engineer* : You're darn right I did!!

# Pharmaceutical Facility Design

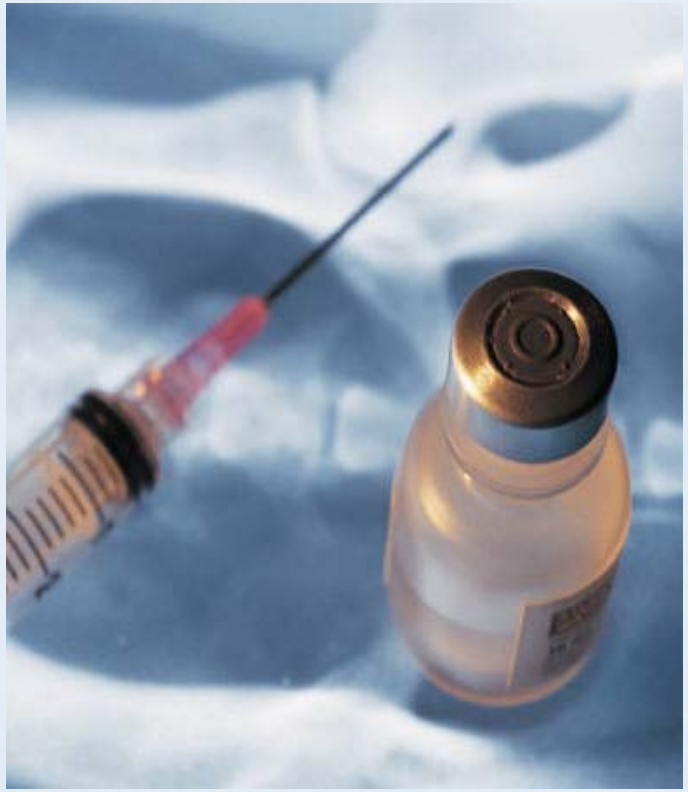
## Purpose:

- Gain a basic understanding of the sterile manufacturing process
  - Vial formulations will be used as the model
- Gain a basic understanding of the equipment used during the manufacturing process.

# Pharmaceutical Facility Design

**Critical Issues:**

- Aseptic Processing
- Terminal Sterilization



# 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

# Sterile Processing

**FDA Aseptic Guidelines –**

Originally published in 1987, Revised in September 2004

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

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

**Note:**

a) These are Guidelines, not regulations.

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

c) As far as manufacturers are concerned, they are as important as the law, since they represent FDA's current thinking and expectations; Aseptic vs. Terminal Sterilization

# 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.

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

- Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. For example, glass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration. Each of these manufacturing processes requires validation and control. Each process could introduce an error that ultimately could lead to the distribution of a contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the possibility of error.

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

- Terminal sterilization usually involves filling and sealing product containers under high-quality environmental conditions. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-process product and to help ensure that the subsequent sterilization process is successful. In most cases, the product, container, and closure have low bioburden, but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat or irradiation.

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

- Sterile drug manufacturers should have a keen awareness of the public health implications of distributing a non-sterile product. Poor cGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient.

# Sterile Processing Example: Vial


# 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

Air-cleanliness and cross-contamination prevention apply to all process steps... and will be discussed in detail later in the course.

# Sterile Processing

## Dispensing:

- Solids: Weigh solids on a scale, in accordance with processing steps. Typically for actives and excipients.
  - Typically performed in a dedicated clean room: “Dispensing Room” (ie: Downflow booth with scale)
- Liquids: Allow liquid to flow into a vessel, determine amount by either flowmeter or vessel mounted load cells – perform weight conversion. Typically water or solvents.
  - Traditionally performed in a “Compounding Room”.

# Sterile Processing

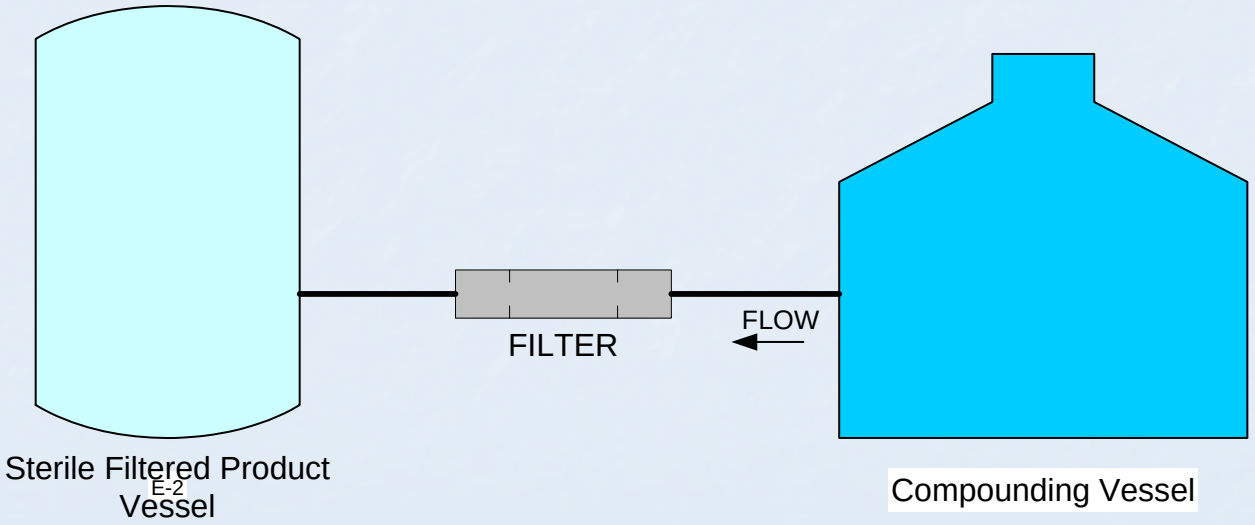
## Compounding

- Bring components together; product, excipient and solvent to create the formulation.
- WFI (Water for Injection) is typically used for aqueous formulations.
- Typically mixed in a vessel
  - Portable tanks typically for smaller batch sizes.
  - Stationary/Fixed tanks typically for larger batch sizes.
- Processing vessels and components are cleaned and sanitized prior to use.

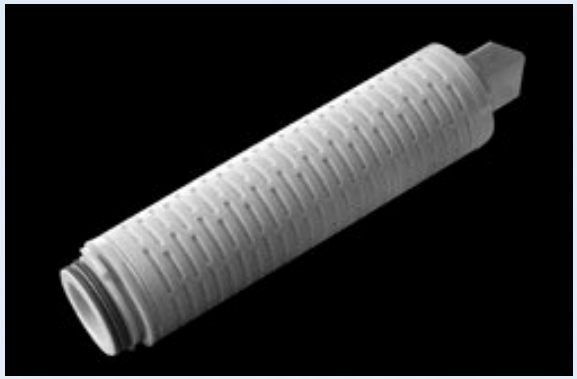
# Sterile Processing

## Filtration (Sterile Filtration)

- Filter the product to render it sterile
- In-line filter typically used between compounding vessel and product vessel



# Sterile Processing



## Filtration (Sterile Filtration)

- Typically a 0.2 micron membrane filter is used
- Filter must be integrity tested before use
- Product is forced from compounding vessel to product vessel – motive force is often pressurized, pure Nitrogen gas
- Filtration is typically in its own separate clean room

- Example: Pall Ultipor® N66 sterilizing grade filter cartridges feature double layer pure Nylon 6,6 membranes for higher assurance of sterilization

# Sterile Processing

## Container Preparation

- Washers typically handle 100 – 400 vials per minute.
- Clean vials are collected, then sterilized in a dry-heat oven.

# Sterile Processing

## Container Preparation

**Sterilization** is typically performed in a Dry-Heat Oven

- Hot, dry air sterilizes the containers
- Reduces both bio-burden load and endotoxin load

# 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 through a “tunnel” with hot air (larger quantities)

# Sterile Processing

## Container Preparation

***The process of cleaning* and s*terilizing* empty product containers.**

# Sterile Processing

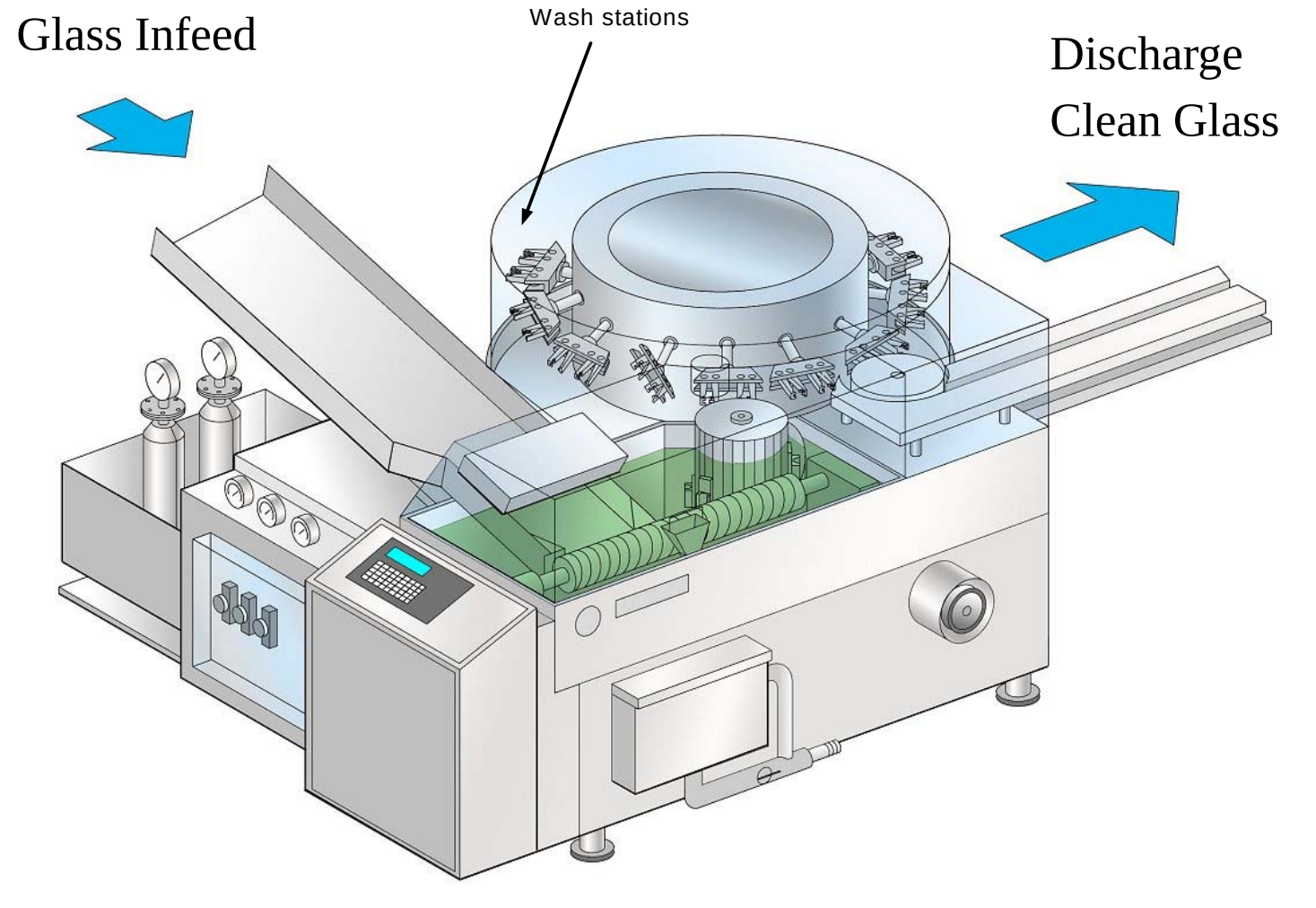
**Cleaning/washing:**

Cleaning via special, elaborate washing machines (glassware washers)

- Removes particulates and chemicals
- Purified Water and WFI are typically used to wash and rinse the containers

# Typical Glass Washer

# Sterile Processing:
# Typical Rotary Glass Washer



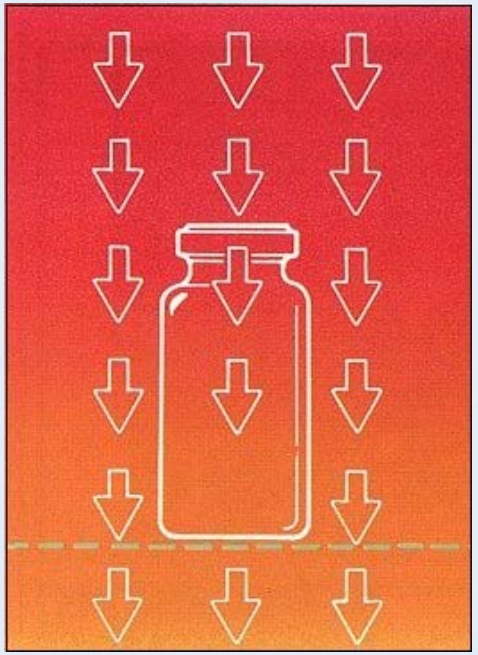
# Sterile Processing

## Container Preparation

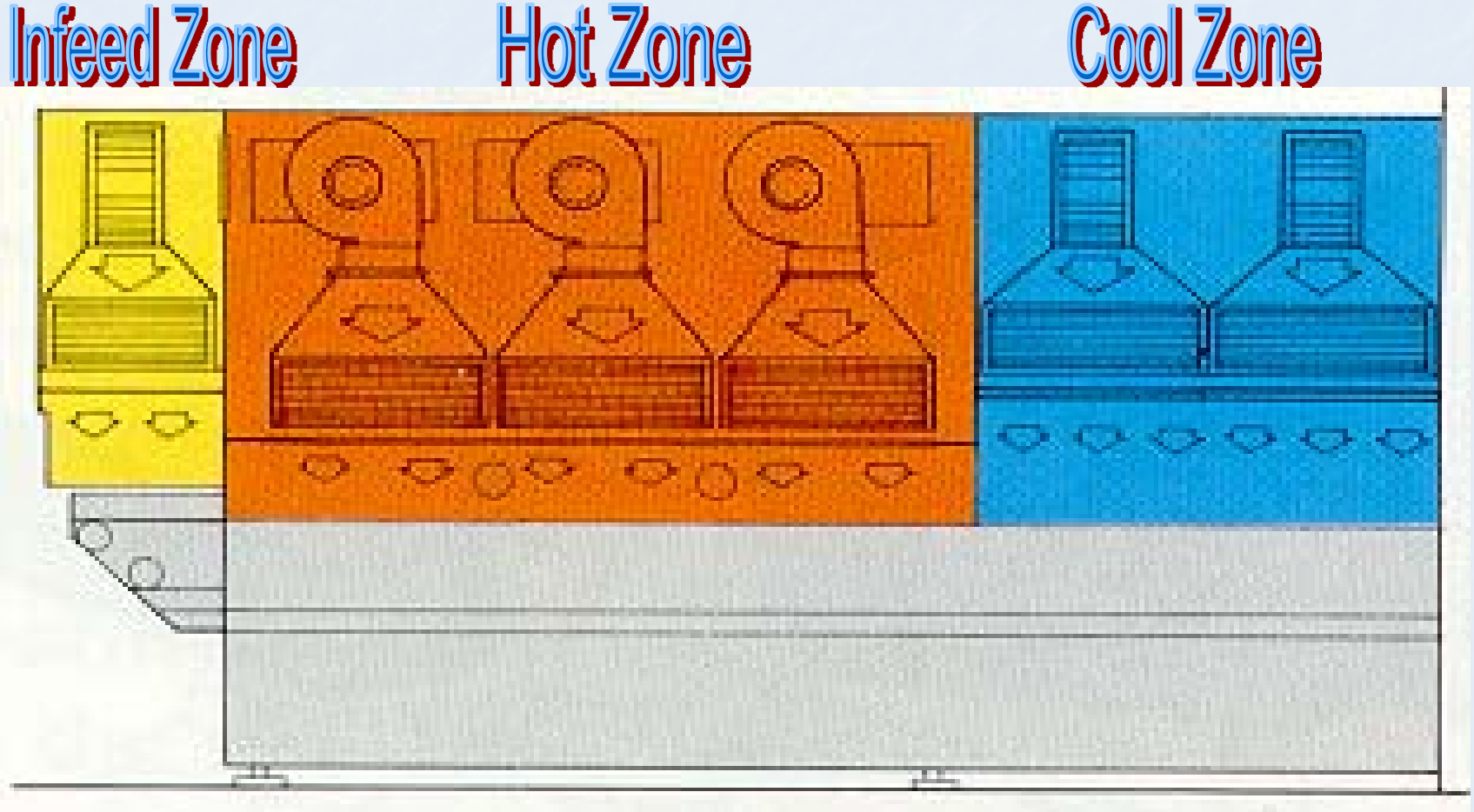
**Depyrogenation Tunnel has three sections:**

- **In-Feed Zone**
- **Hot-Zone**
- **Cool-Down Zone**

**Vials travel on a wide belt**

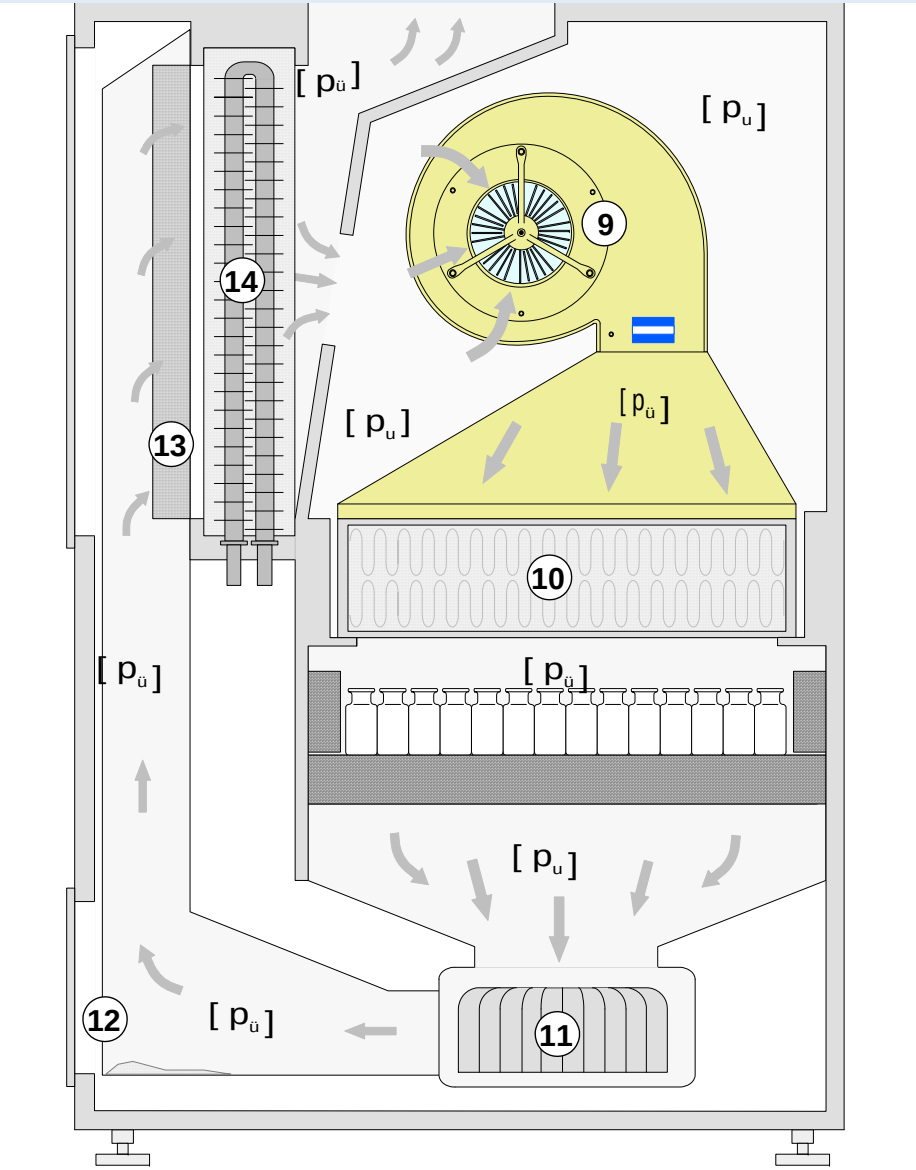


# Depyrogenation Tunnel

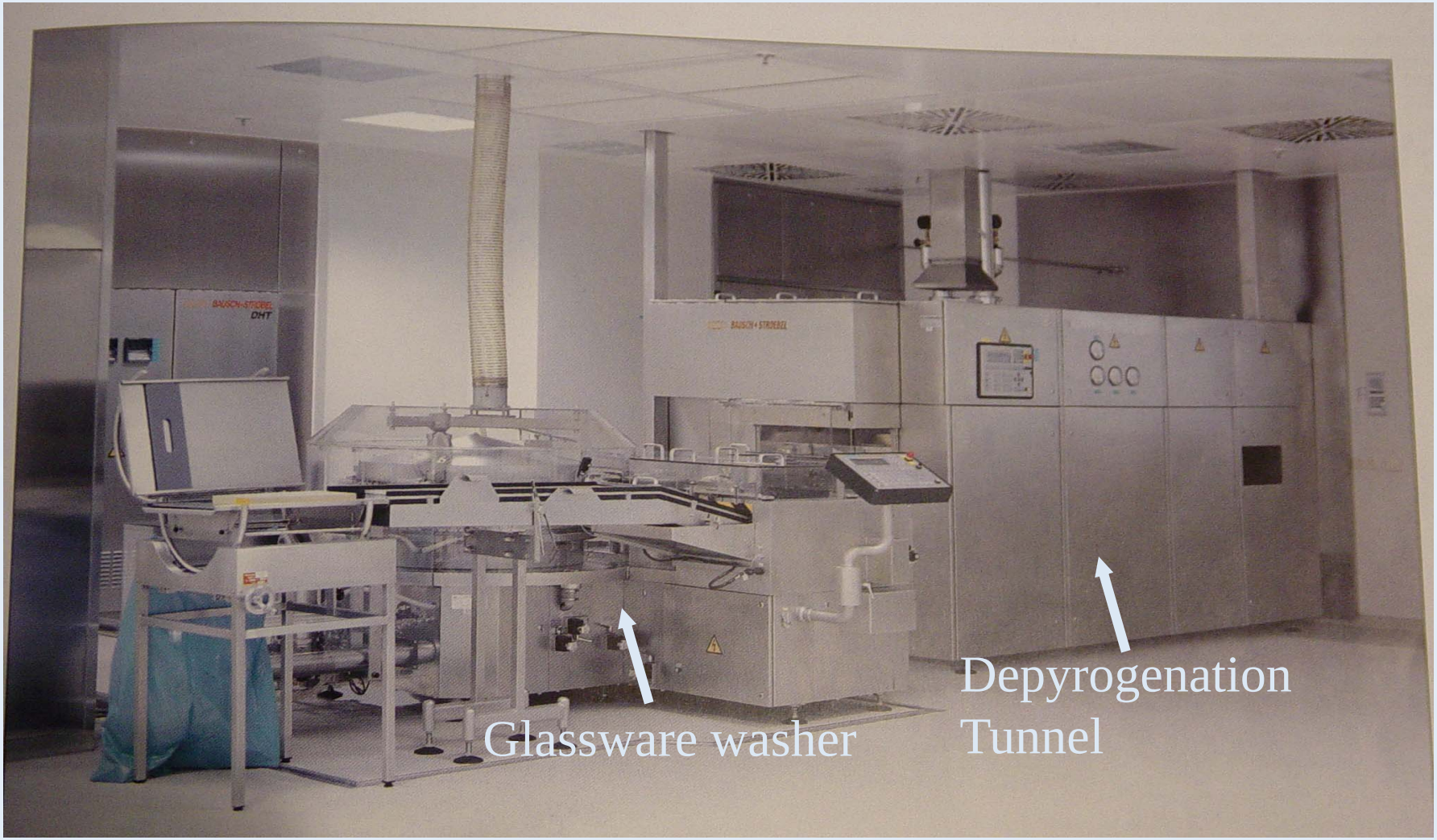


# Sterile Processing

- Vials line-up on a belt
- Vials travel through all zones
- Hot Zone temperature typically in the 300 °C range



# Depyrogenation Tunnel



# 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

## Component Sterilization

- **Saturated steam autoclaves are most common:**
  - Typically require 121 °C for sterilization, equivalent to approximately 28 psig.
  - The steam comes from a clean steam generator.
  - With saturated steam autoclaves, air must be evacuated.
    - **Air insulates and prevents lethality by saturated steam**

# Sterile Processing

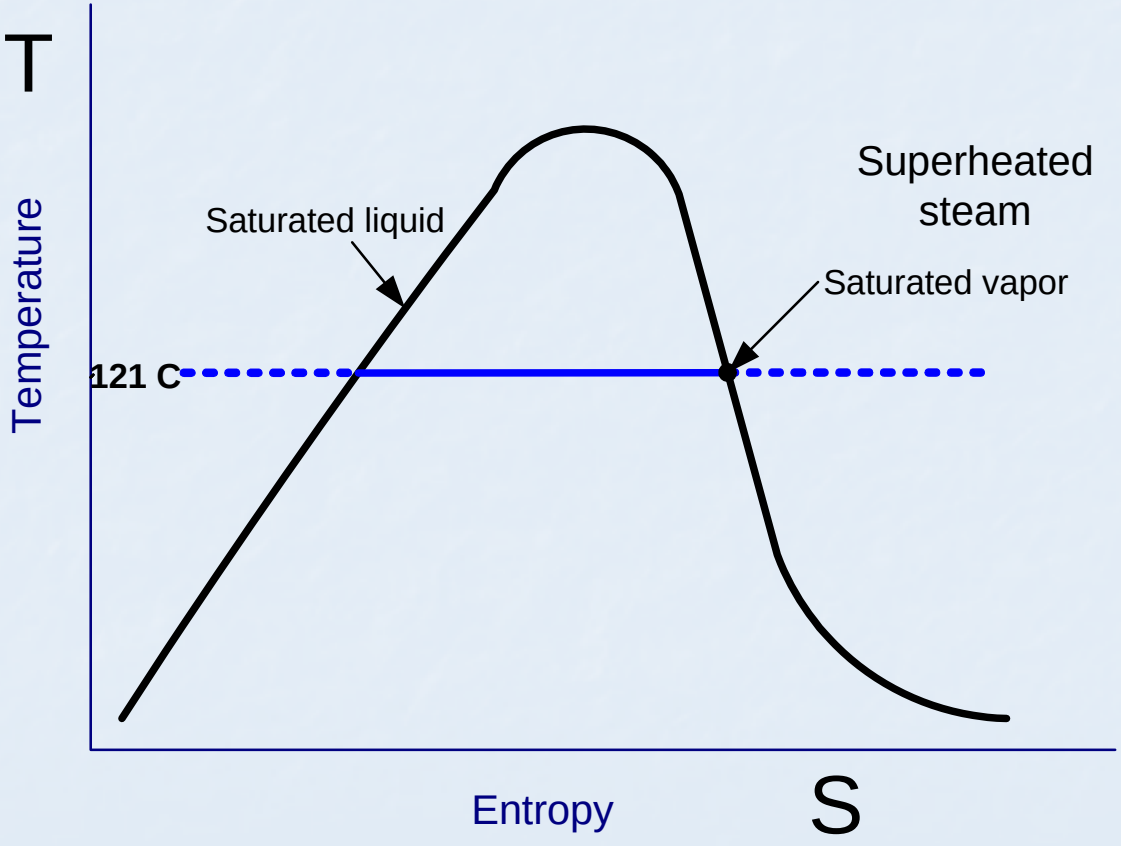
## Component Sterilization

**Steam Sterilization:**

- Steam sterilization occurs when saturated steam contacts a surface or organism.
- More effective than superheated steam?
  - Why? Superheated steam is at a higher temperature?
  - You need the liquid phase to help break down the proteins in the cell wall of the organism.

# Sterile Processing

Raising the temperature of the steam will change the steam to the superheated phase - less effective at killing the organisms



# Sterile Processing

## Stopper (Closure) Preparation:

- Like the container and product contact parts, closures (stoppers) must be sterile, and free of contaminants
- Stoppers must be washed to remove particulate matter
  - Typically washed in a stopper washer with mechanical agitation (ie: rotating drum)
- After washing, stoppers are rinsed
- Stoppers are then sterilized.
  - Option #1: Stopper washer with a sterilization cycle
    - Preferred
  - Option #2: Autoclave

# Sterile Processing

## Stopper (Closure) Preparation:

- **After sterilization, stoppers are typically lubricated, by silicone application.**
  - Care must be exercised with silicone levels as too much silicone can result in particulate formation
- **Air drying is final step.**

## Notes:

- **Cleaning agents are sometimes used.**
  - If agents are used, must ensure full removal of agent by checking the quality (conductivity) of the rinse water if appropriate.

# 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

**Filling Operation:**

- Different types of methods for filling
- Most common method of filling is piston pump and time-pressure
- Since you want to stopper the product ASAP, filling machines come with stoppering stations
- Stoppers are fed typically into a vibratory bowl, which orients the stoppers
- Deoxygenation - For oxygen sensitive products, filling machines often allow for Nitrogen injection on the head space in vial to limit intrusion of oxygen

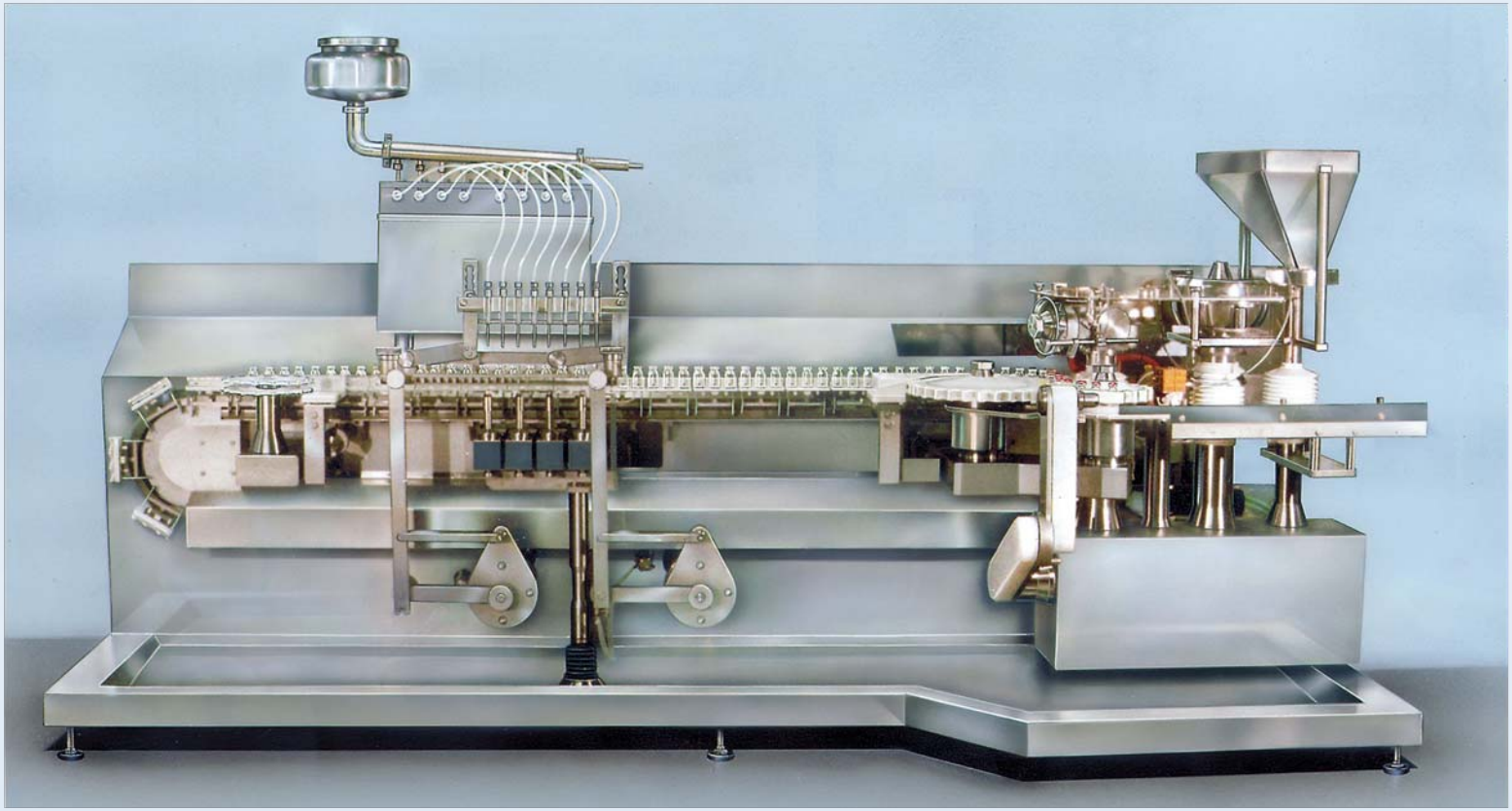
# Sterile Processing

## Filling Operation

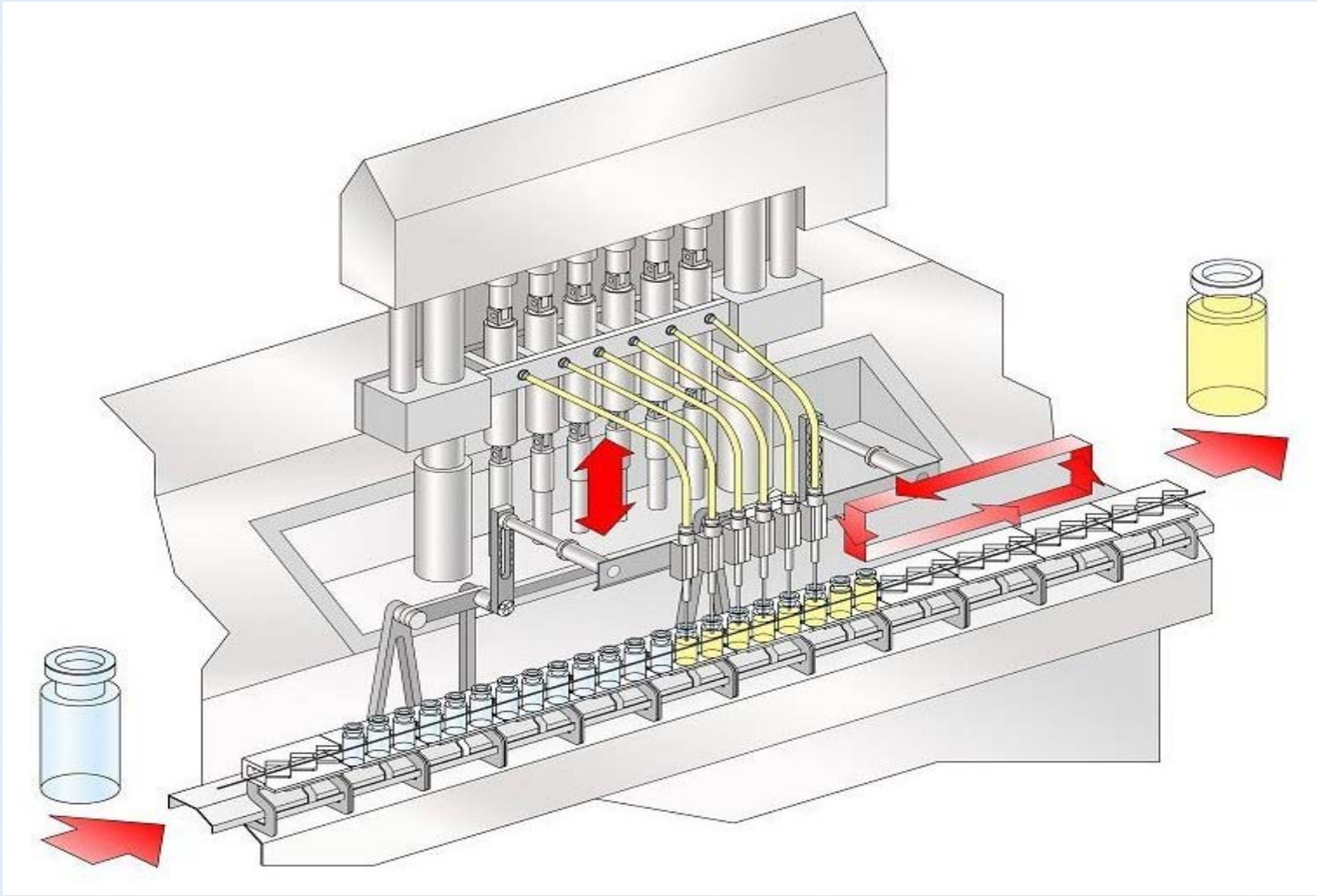
- For lyophilizer stoppers, height of stoppering tool is pre-adjusted to ensure stoppers are not fully seated.
- Filling machines are rated at containers filled per minute. (ie: Vials per Minute or VPM)
- Product and container closure contact parts must be able to withstand repeated cleaning and sterilization
- Fill checks should occur automatically with a certain number of vials taken off line to be checked for fill weight, and then returned to line, as part of In-Process Controls, or IPC.

# Sterile Processing

**Filling Operation:** Typical filling machine

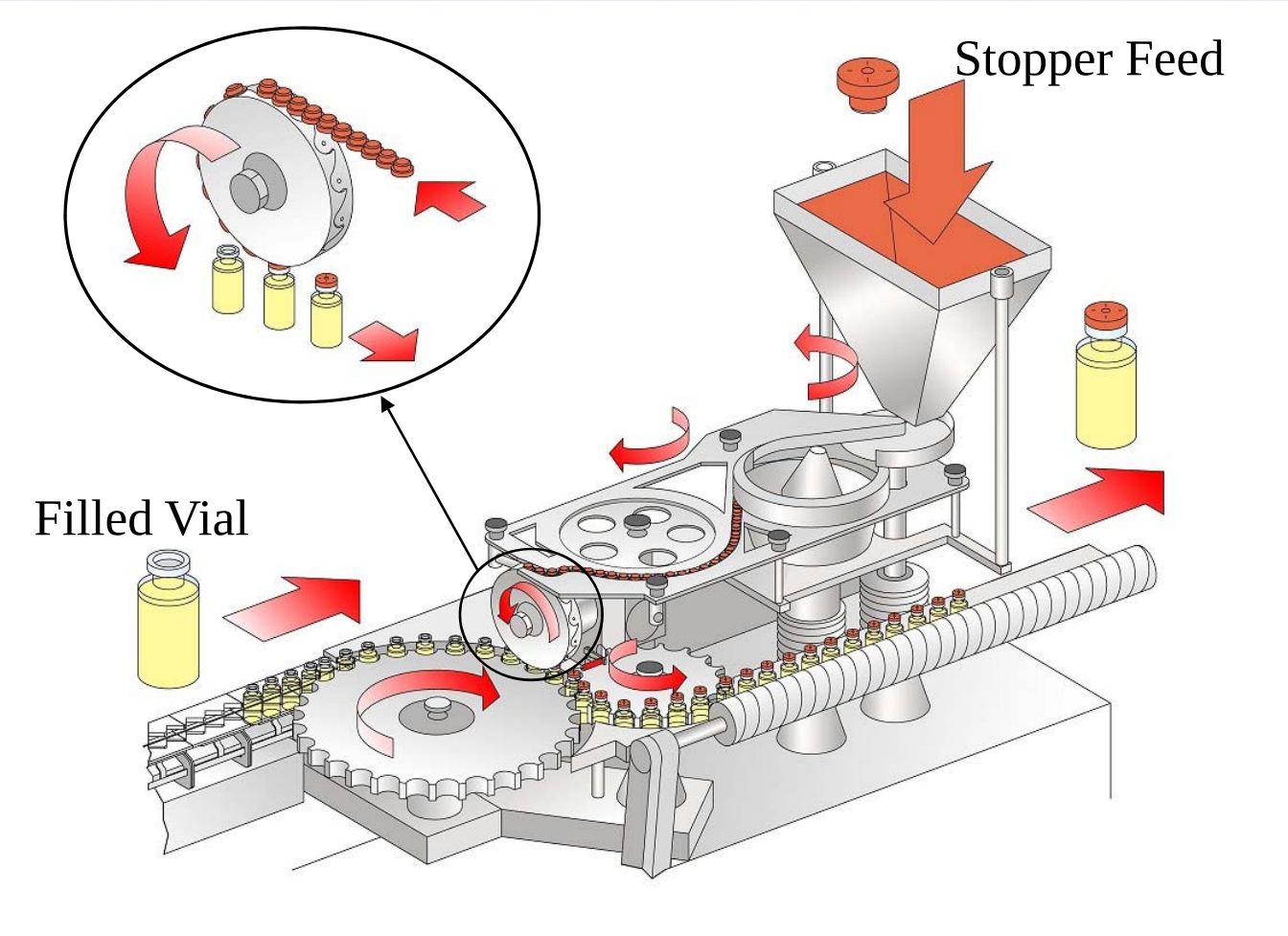


# Sterile Processing – Vial Filling



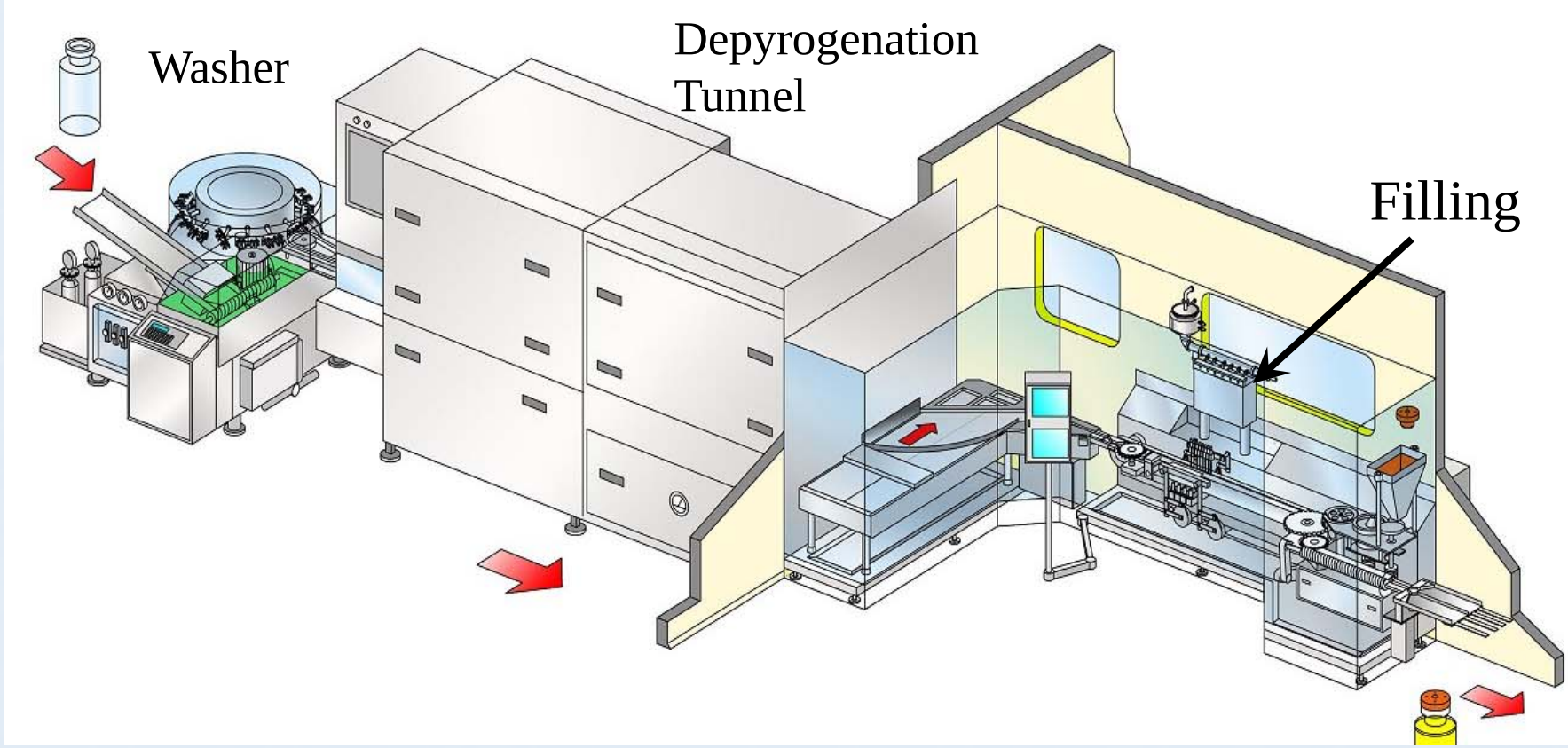
# Sterile Processing

Filling machines also stopper the vials after filling



# Sterile Processing

Process with washing, depyrogenation, filling & stoppering



# 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

Lyophilizer shelves are filled with vials that follow a three step process:

1. Freezing: Product is frozen by cool fluid flowing through the shelves
2. Primary Drying: Product is heated by gradually heating the shelves so water vapor escapes while vacuum is pulled in the lyophilizer chamber
3. Secondary Drying: Product temperature is gradually raised as vacuum levels are maintained, further drying the product

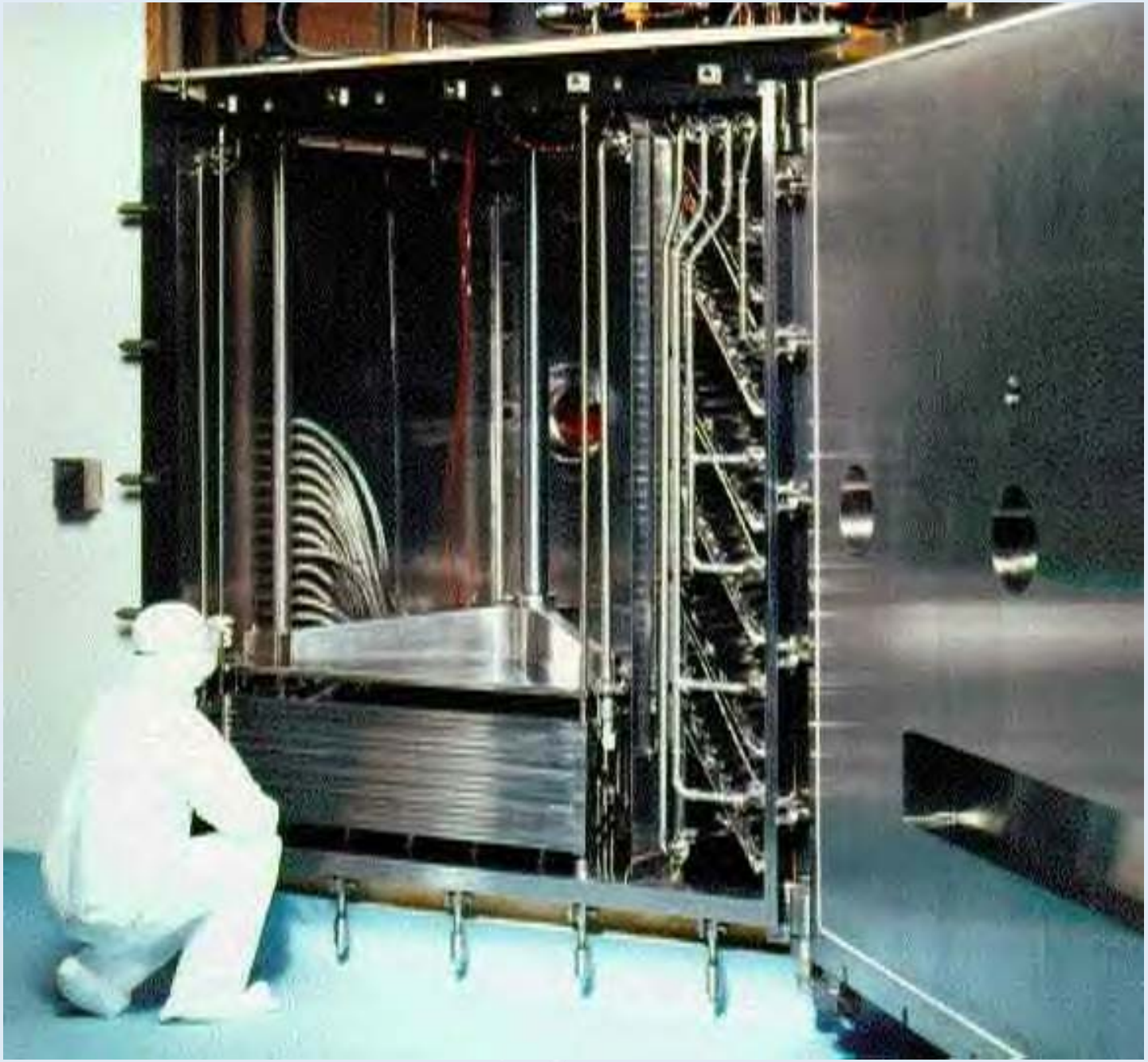
# Sterile Processing

Operator manually loading a tray into the lyophilizer.

# Sterile Processing

# Sterile Processing

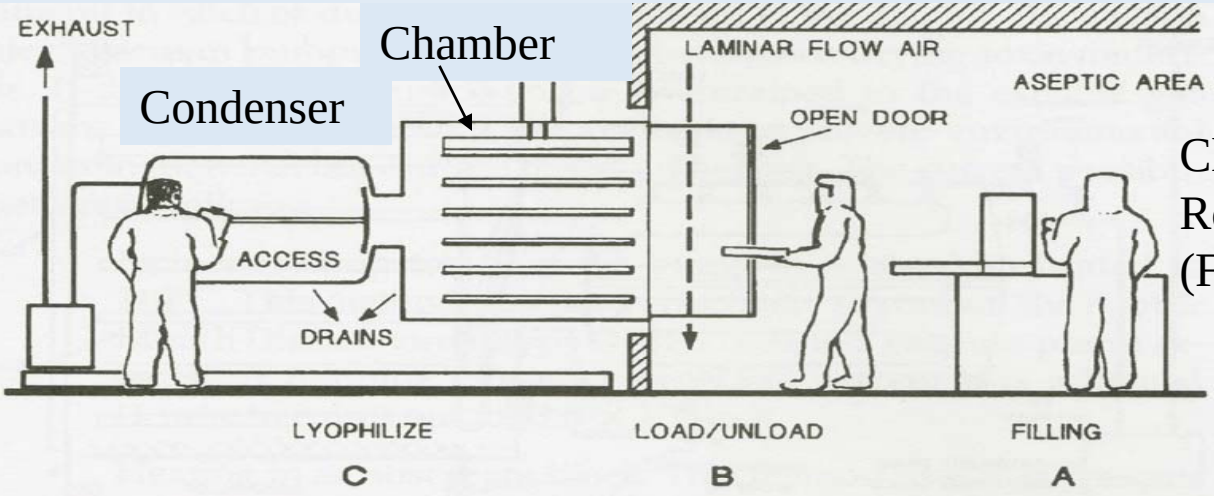
Once secondary drying is complete, shelves are collapsed by a hydraulic ram, to fully stopper the vials.



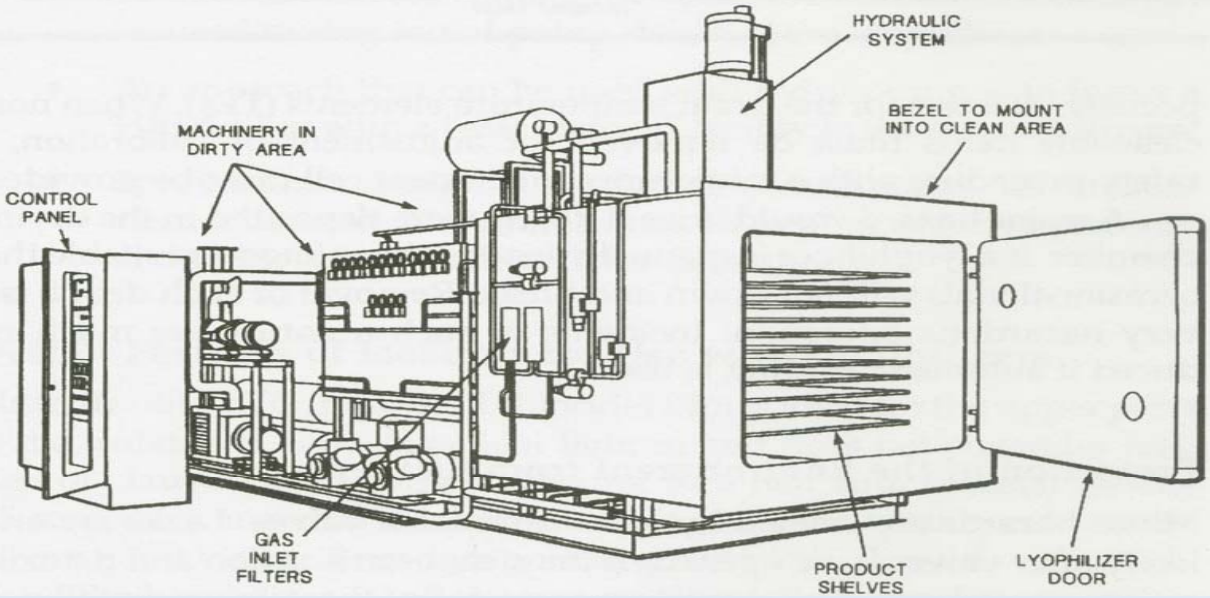
# Sterile Processing

**Main components of a lyophilizer**

- Chamber
- Condenser
- Refrigeration and heating skid




# Lyophilizer Components



# Sterile Processing

**Lyophilization Unique Issues:**

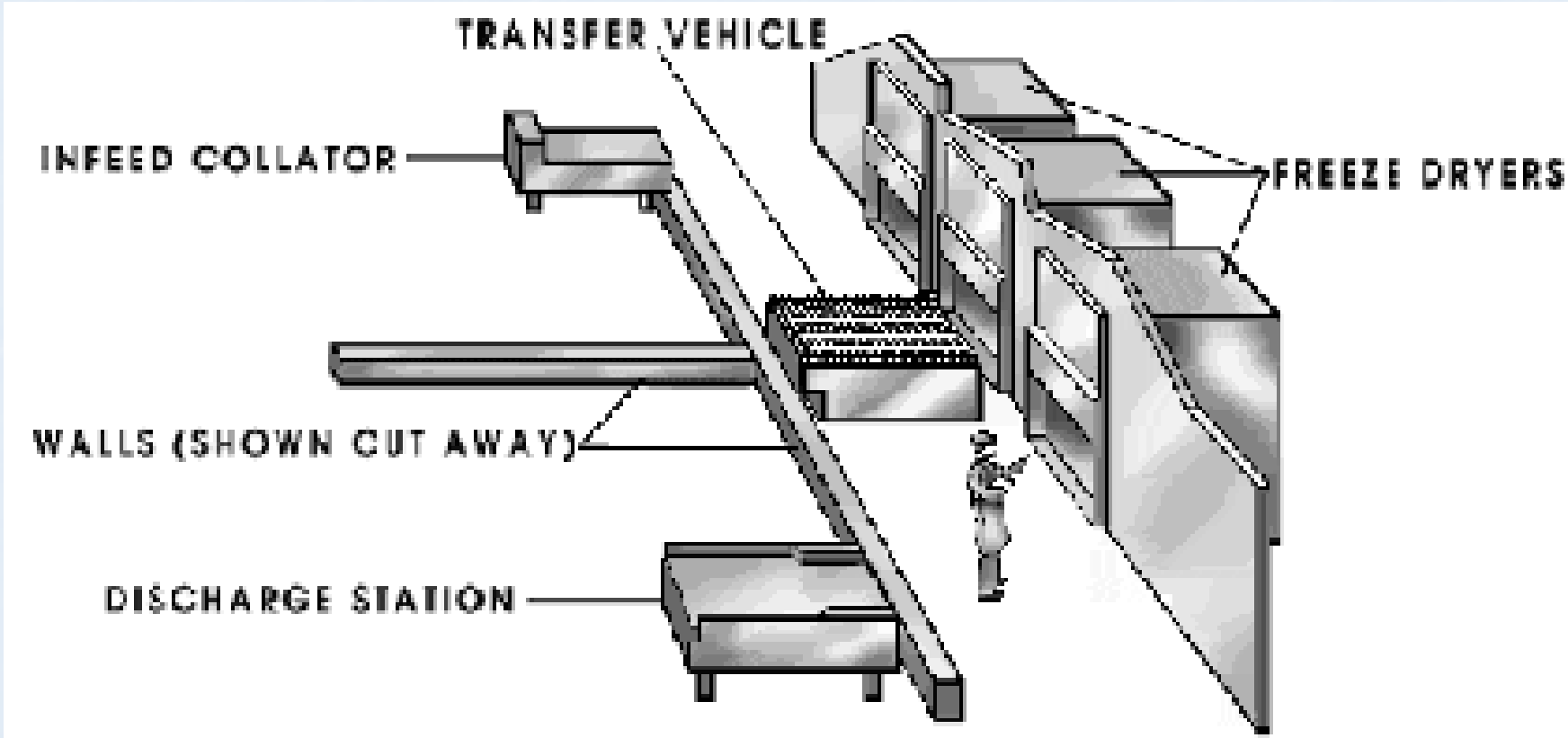
- Refrigeration skid requires cooling, typically chilled water
- Very large equipment
- Very energy intensive
- Leaks are a major concern, since product is exposed and a deep vacuum is drawn
- Must have trained personnel due to the relative complexity of the equipment
- Requires very long cycles

# Sterile Processing

**Lyophilization Loading:**

- Can be done manually via trays holding glassware
- Automatic loading available is available but very expensive and complex.
  - Makes sense for large quantities only

# Sterile Processing
# Automatic Lyophilizer Loading



# Sterile Processing

**Capping**

**(Capping & Crimping)**

- Purpose is to ensure the inserted stopper in the vial neck is secured to assure the long term integrity and sterility of the vial
- Machine places the cap on the vial, then secures it with an aluminum crimp.
- Crimping generates particulate, therefore capping occurs typically in a separate room

# Capper

# Sterile Processing

## Non-Lyophilizer

- Inspection to check for particulates and foreign matter required by USP.
  - Visual inspection using the human eye
  - Automated inspection using electronic imaging or light-scattering techniques

# Automated Inspection

Inspection Machine

# Sterile Processing

## Non-Lyophilizer

**Terminal sterilization**

- Sealed product is sterilized in an autoclave
- Typically steam sterilization
- After sterilization, product proceeds to inspection

# Sterile Processing

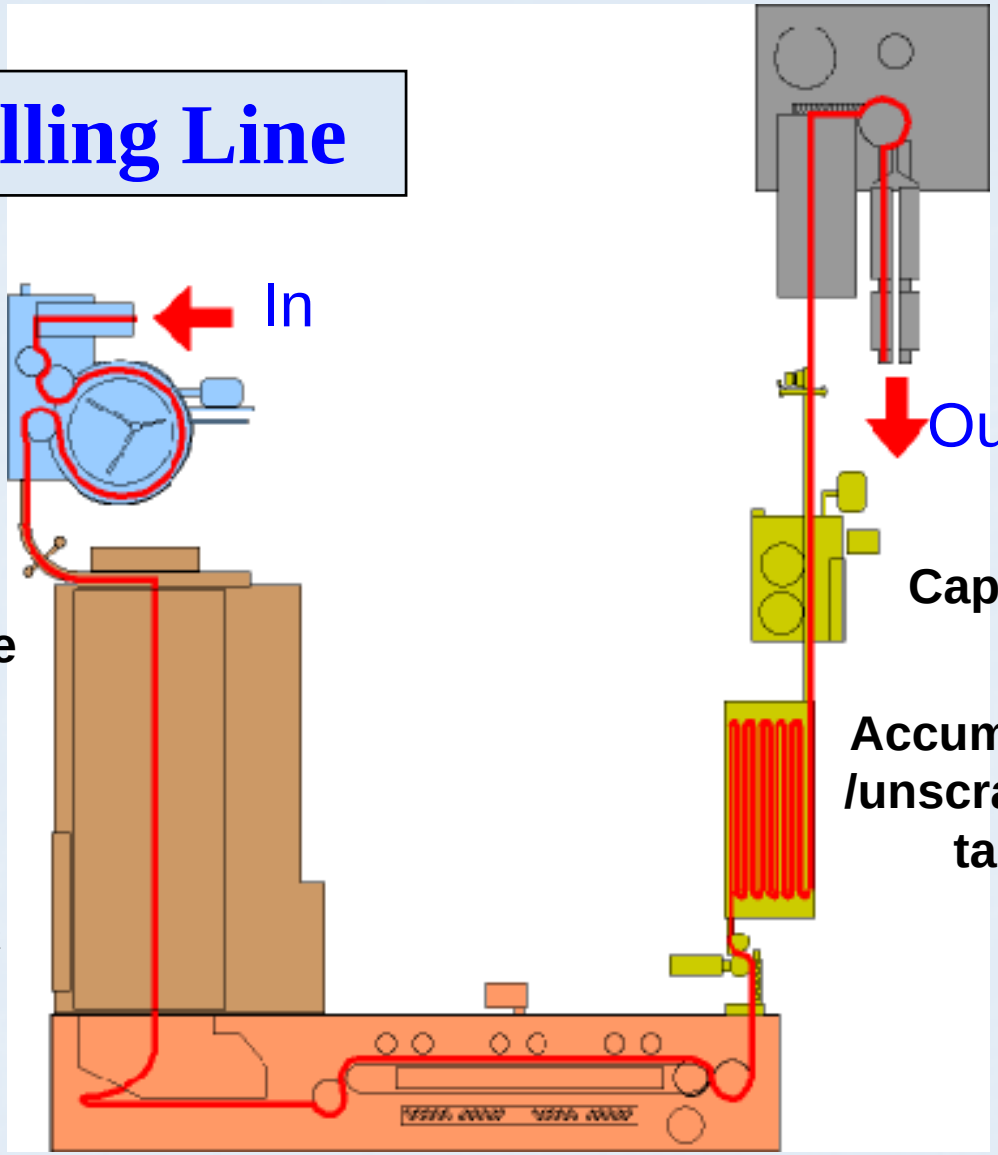
## Non-Lyophilizer

**After final inspections:**

- Labeling and final packaging

# Labeling Machine

# Vial Filling Line




Wash

Depyrogenate /sterilize

Fill and stopper

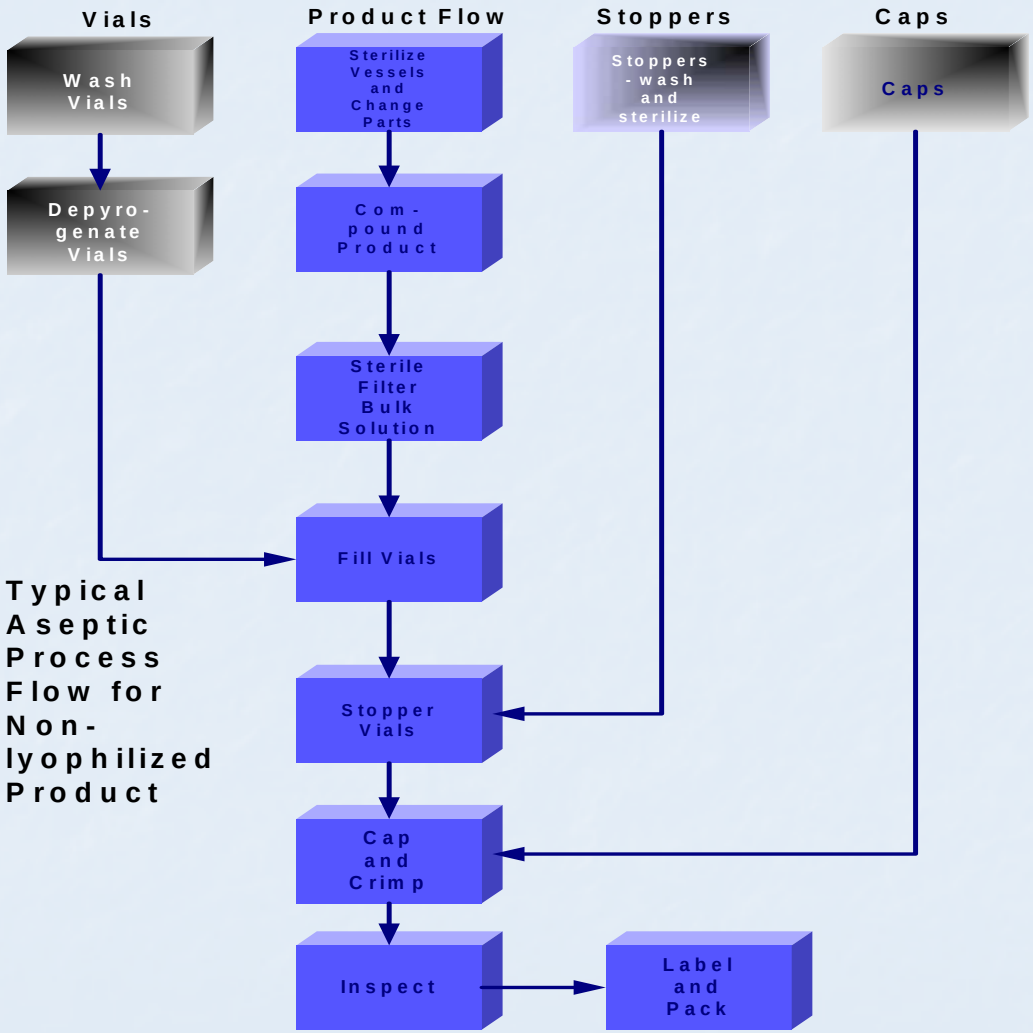
Capping

Labelling

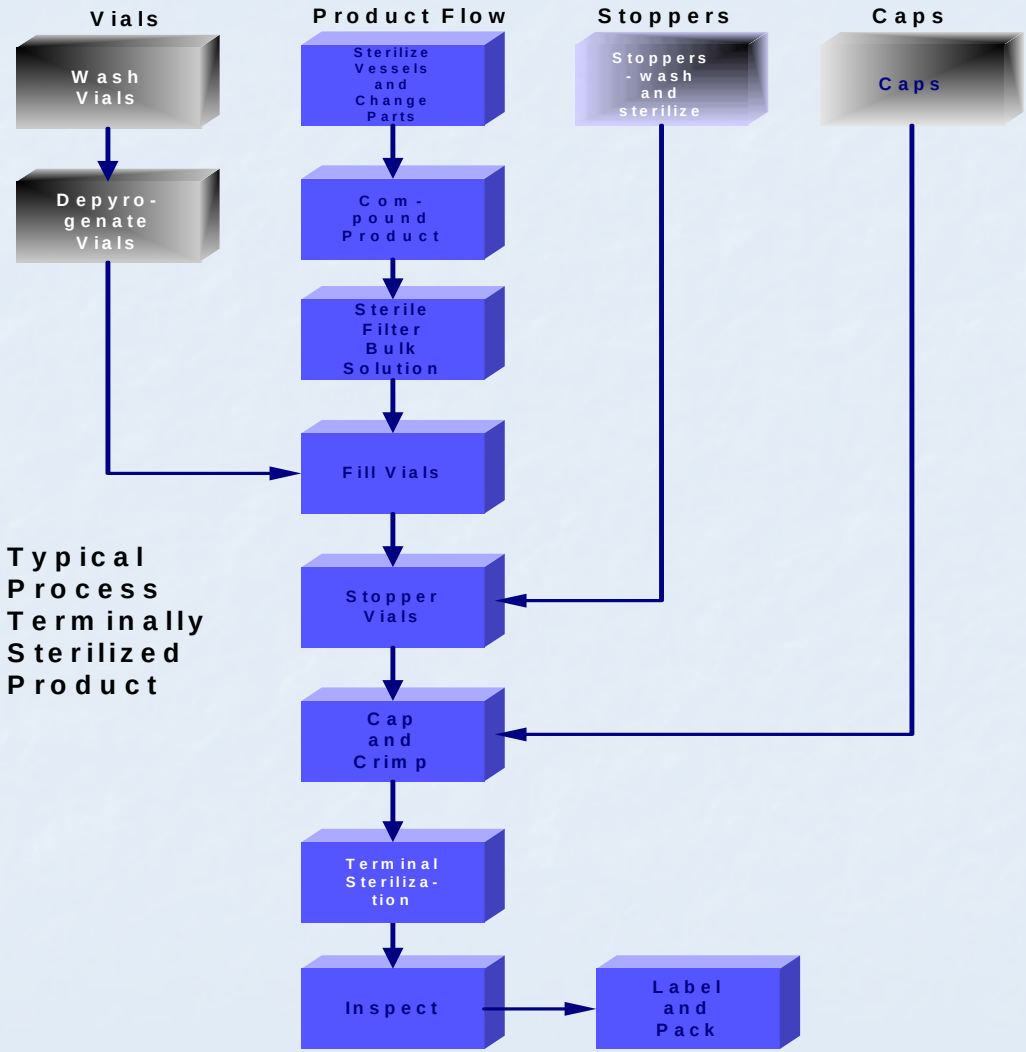
Accumulation /unscrambling table

Note: Inspection stage not shown on this line

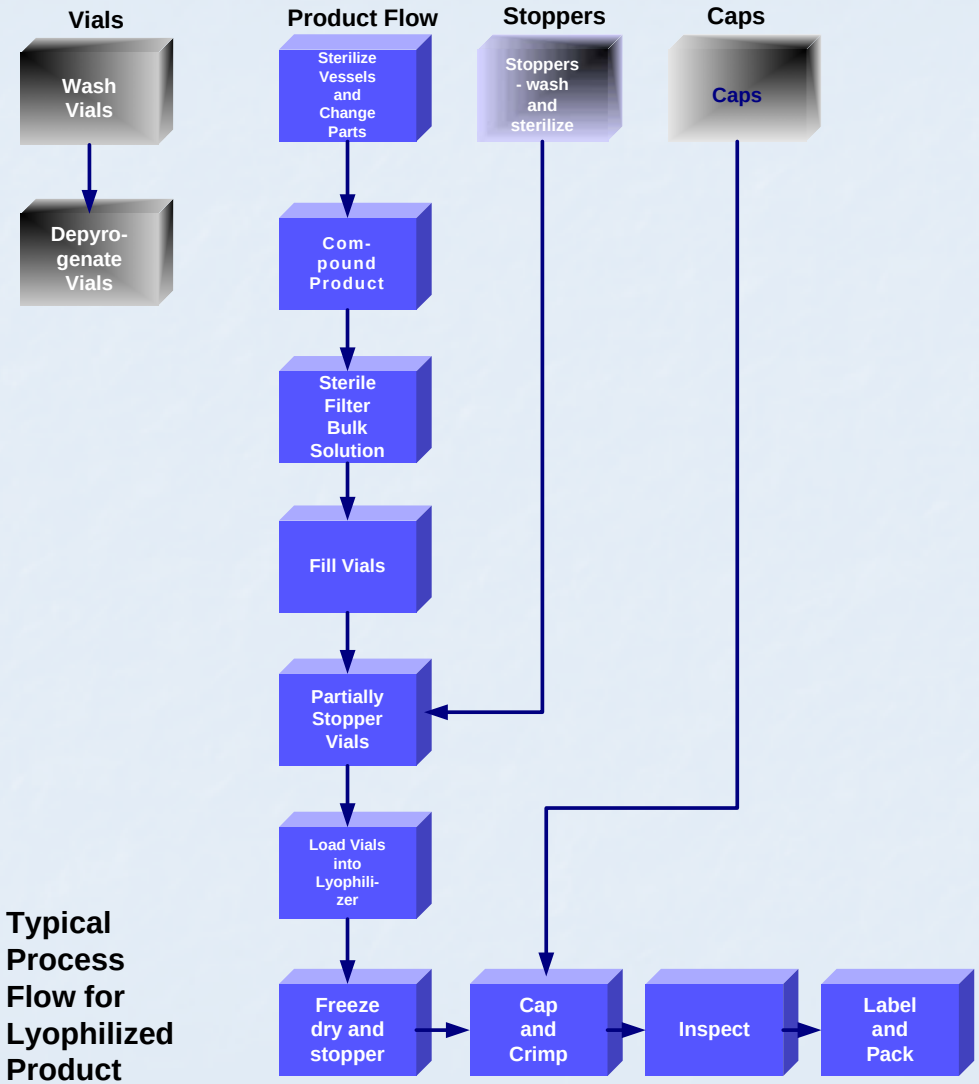
# Sterile Processing – Non-Lyo



# Sterile Processing – TS Product



# Sterile Processing - Lyo




**Typical Process Flow for Lyophilized Product**