


Introduction to the  
Pharmaceutical Industry

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Drug Manufacturing

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## Manufacturing Facilities

- ◆ Active Pharmaceutical Ingredients (APIs)
  - APIs are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

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## Chemical API Manufacturing



4



## Biotech APIs produced by cell culture and/or fermentation




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## Dosage Form Manufacturing

- ◆ A brief review of the various dosage forms supplied by pharmaceutical manufacturers

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## Oral – tablets, capsules and liquids



Tablets versus Pills?

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## Topical – creams and ointments (may be sterile)



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# Ophthalmic – drops (sterile)

9

# Otic – ear drops (sterile)

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# suppositories

**GlaxoSmithKline UK**

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Uxbridge  
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Document last updated on the eMC: **Mon 10 March 2003**


Zofran Suppositories 16mg ▼

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# Injectables (sterile)





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inhalants (sterile)



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This slide features a blue background with a vertical yellow and orange gradient bar on the left containing a metal key. The title 'inhalants (sterile)' is written in yellow text. Two images are shown: a blue nebulizer device and a box of Albuterol Sulfate Inhalation Solution (0.083%) with a blister pack of four 2 mL vials.

Large Volume Parenterals



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This slide features a blue background with a vertical yellow and orange gradient bar on the left containing a metal key. The title 'Large Volume Parenterals' is written in yellow text. An image shows a clear plastic IV drip chamber hanging from a metal stand.



## FDA's Role in the Design and Operation of Facilities and Equipment

- ◆ Pertinent GMPs

(GMPs are Law!)

(The cGMPs)


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## § 210.1 Status of current good manufacturing practice regulations

- ◆ to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. (Design and construction can affect quality and purity.)


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§ 211.42 Design and construction features.

- ◆ (a) Buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.


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§ 211.42 Design and construction features. (continued)

- ◆ (b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups .... and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.


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§ 211.46 Ventilation, air filtration, air heating and cooling. (continued)

- ◆ (a) Adequate ventilation shall be provided.
- ◆ (b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.


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§ 211.46 Ventilation, air filtration, air heating and cooling. (continued)

- ◆ (d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.  
(Anaphylactic shock - ~3% mortality rate)


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## § 211.56 Sanitation.

- ◆ (a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation .... Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

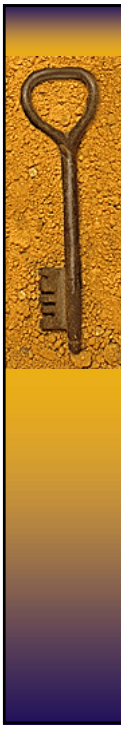
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## § 211.56 Sanitation (continued)

- ◆ (b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

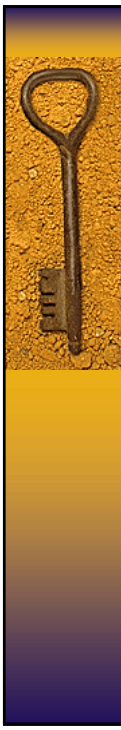
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## § 211.56 Sanitation (continued)

- ◆ (c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination .....
- ◆ (d) Sanitation procedures shall apply to work performed by contractors or temporary employees.....


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## § 211.65 Equipment construction.

- ◆ (a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product ....


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§ 211.65 Equipment construction. (continued)

- ◆ (b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product ....


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Components and Drug Product Containers and Closures:  
§ 211.80 General requirements.

- ◆ (b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.


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§ 211.84 Testing and approval or rejection of components, drug product containers, and closures.

- ◆ (a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

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§ 211.113 Control of microbiological contamination.

- ◆ (a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

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## § 211.113 Control of microbiological contamination. (continued)

- (b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

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## § 211.130 Packaging and labeling operations.

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products...

- ◆ (a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.


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# FDA's Role in the Design and Operation of Facilities and Equipment

◆ FDA Guidance documents

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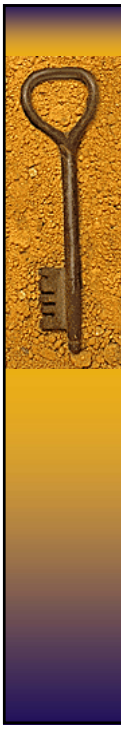
# FDA Guidance documents

	<b>Office of Regulatory Affairs</b> <b>Inspection References:</b> <b>Inspection Guides</b>	
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<ul style="list-style-type: none"> <li><a href="#">ORA Site QuickNav</a></li> <li><a href="#">Inspection References</a></li> <li><a href="#">Field Management Directives</a></li> <li><a href="#">Guides to Inspections of...</a></li> <li><a href="#">IOM: Investigations Operations Manual</a></li> <li><a href="#">International Inspection Manual &amp; Travel Guide</a></li> <li><a href="#">Inspection Technical Guides</a></li> <li><a href="#">GMP Reference (CDRH)</a></li> <li><a href="#">OS REGULATION/DESIGN CONTROLS</a></li> </ul>	<p style="text-align: center;"><b>Guide to Inspections of:</b></p> <ul style="list-style-type: none"> <li>• <a href="#">Biotechnology</a></li> <li>• <a href="#">Biologics</a></li> <li>• <a href="#">Computer Issues</a></li> <li>• <a href="#">Devices</a></li> <li>• <a href="#">Drugs</a></li> <li>• <a href="#">Foods/Cosmetics</a></li> <li>• <a href="#">Miscellaneous</a></li> </ul> <p style="font-size: small;">Note: These documents are reference material for investigators and other FDA personnel. The documents do not bind FDA and do not confer any rights, privileges, benefits or immunities for or on any person(s). An alternative approach may be used if such an approach satisfies the applicable statutes, regulations or both.</p> <p style="text-align: center; font-size: small;">Updated: April 2001</p>
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[http://www.fda.gov/ora/inspect\\_ref/igs/iglist.html](http://www.fda.gov/ora/inspect_ref/igs/iglist.html)

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## FDA Guidance documents




**FDA** U.S. Food and Drug Administration   
Department of Health and Human Services

CENTER FOR DRUG EVALUATION AND RESEARCH

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**Guidance for Industry**

**Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice**

***DRAFT GUIDANCE***

This guidance document is being distributed for comment purposes only.

<http://www.fda.gov/cder/guidance/1874dft.htm>

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## FDA Guidance documents

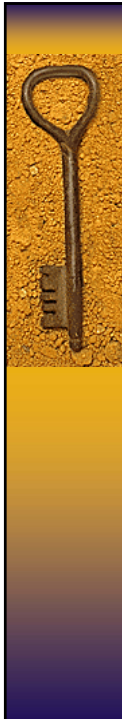
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### **Guidance for Industry**

### **Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients**

<http://www.fda.gov/cber/gdlns/ichactive.pdf>

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## Facilities, Equipment and Systems for Pharmaceutical Processes

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## Oral & Topical Products (Tablets) – Basic Operations

- ◆ Formulation
- ◆ Compression
- ◆ Packaging

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## Oral & Topical Products (Tablets) – Formulation

- ◆ Objective is to obtain a uniform mixture that can be compressed.
  - Dry Granulation – Twin Shell Blender
  - Wet granulation – Fluid Bed Granulator
  - Milling

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## Oral & Topical Products (Tablets) – Formulation – Small Twin Shell Blender



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Oral & Topical Products  
(Tablets) – Formulation  
Fluid Bed  
Granulator



Dust Explosion  
Hazard –  
Pressure Relief  
Panels



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Oral & Topical Products  
(Tablets) – Formulation - Milling



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## Oral & Topical Products (Tablets) – Compression

- ◆ Objective is to compress a uniform mixture into tablets that dissolve in a uniform manner.
  - Tablet Press

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## Oral & Topical Products (Tablets) – Compression



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Oral & Topical Products  
(Tablets) – Compression



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Oral & Topical Products  
(Capsules) – Capsule Filler



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## Oral & Topical Products (Tablets & Capsules) – Packaging

- ◆ Objectives
  - accurately count a given quantity of tablets or capsules into a bottle
  - Insert cotton – if required
  - Place inner seal – if required
  - Screw on cap
  - Install security band

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## Oral & Topical Products (Tablets & Capsules) – Packaging

- ◆ Objectives (continued)
  - Attach label to bottle
  - Place bottle and leaflet into carton and close carton
  - Place cartons in shipping carton
  - Tape shipping carton
  - Label shipping carton

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## Oral & Topical Products (Tablets & Capsules) – Packaging

- ◆ New Jersey Machine Company  
<http://www.newjerseymachine.com>



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## Oral & Topical Products (Tablets & Capsules) –Facilities

- ◆ Objectives
  - Prevent Contamination - Cleanability
  - Avoid Mixups - Segregation
  - Control Cross Contamination – Containment, Dust Collectors, Differential Pressure, Airlocks & Barrier/Isolators
    - Toxicity
    - Potency

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## Oral & Topical Products (Tablets & Capsules) –Facilities

- ◆ Prevent Contamination - Cleanability
  - Non-porous & smooth surfaces with details that minimize dust accumulation
  - Coved floor bases and corners should be considered – not required
  - Horizontal surfaces accessible for cleaning

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## Oral & Topical Products (Tablets & Capsules) –Facilities - Cleanable



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## Oral & Topical Products (Tablets & Capsules) –Facilities - Cleanable



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## Oral & Topical Products (Tablets & Capsules) –Cleanability

- ◆ Packaging area cleanability is less critical than for formulation and compressing operations as minimal product dust is present.

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## Oral & Topical Products (Tablets & Capsules) –Facilities

- ◆ Avoid Mixups - Segregation
  - If more than one product can be formulated and/or compressed at the same time, there must be segregation between different products and different lots of the same product.
    - Walls and doors
    - Corridors

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## Oral & Topical Products (Tablets & Capsules) –Facilities

- ◆ Avoid Mixups - Segregation
  - Packaging lines may be in the same room, but physical separation – chest-high partitions that go to the floor – should separate one line from another.

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## Oral & Topical Products (Tablets & Capsules) –Facilities & Equipment

- ◆ Prevent Cross Contamination –
  - Plan pathways for both people and equipment contaminated with product A that do not pass by people and equipment working with product B and vice versa.
  - This is a potential problem with powders, but less likely to be a problem with liquids.

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## Oral & Topical Products (Tablets & Capsules) –Facilities & Equipment

Prevent Cross Contamination

Containment



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## Oral & Topical Products (Tablets & Capsules) –Facilities & Equipment

Prevent Cross Contamination

Isolator



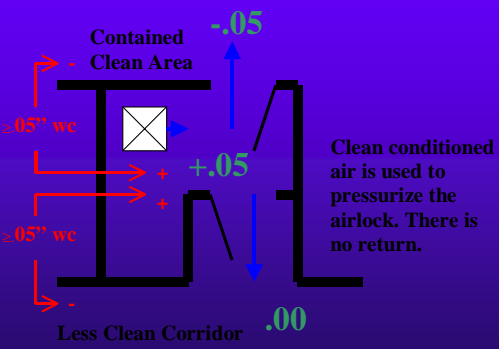
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## Oral & Topical Products (Tablets & Capsules) –Facilities & Equipment

Prevent Cross Contamination

Differential Pressure and Airlock



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## Oral & Topical Products (Liquids) – Basic Operations

- ◆ Formulation
- ◆ Filling
- ◆ Packaging

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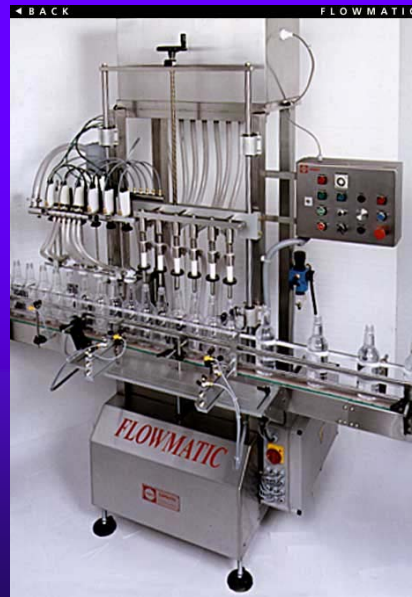


## Oral & Topical Products (Liquids) – Filling

- ◆ Filling Equipment with
  - Positive Displacement Pumps
  - Time-Pressure Filling

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## Oral & Topical Products (Liquids) Filling



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## Oral & Topical Products (Liquids) – Formulation



- ◆ Stainless Steel tanks and mixers
- ◆ Open & Closed Systems
- ◆ Clean-in-Place Systems

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## Oral & Topical Products (Liquids) – Formulation



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## Oral & Topical Products (Liquids) – Packaging

- ◆ Similar to tablet packaging
  - liquid filler in place of tablet counter
  - No cotton inserter

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## Oral & Topical Products (Liquids) – Facilities

- ◆ Similar to tablet facilities
  - Cross contamination not as much of an issue because there is no dust.
  - Aerosols in the vicinity of a filling operation can be an issue if product is toxic or potent.
    - Local air exhaust if product is mildly potent
    - Isolating enclosure for highly potent and toxic products

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## Sterile Products – Basic Operations

- ◆ Formulation
- ◆ Product Sterilization
- ◆ Filling
- ◆ Lyophilization (Freeze Drying)
- ◆ Packaging

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## Sterile Products – Formulation

- ◆ Similar to Non-Sterile Liquid Products except that cleanliness level is increased dramatically.
  - Control of particulates
  - Control of microorganisms
  - Increased control of cross contamination
  - Increased concern that materials will leach into product


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## Sterile Products – Basic Operations - Formulation

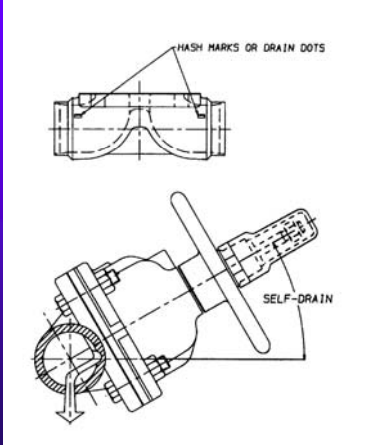
- ◆ Type 316L Stainless Steel tanks and piping with specialized surface finish.
- ◆ Diaphragm Valves
- ◆ Class 10,000 Environment

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## Sterile Products – Basic Operations - Formulation

- ◆ Diaphragm Valves



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## Sterile Products – Basic Operations - Classified Environments

U.S. Class – Particles per Cubic Foot (5 microns and larger)	CFU per 10 Cubic Feet of Air
<b>100</b>	<b>Less than 1</b>
<b>10,000</b>	<b>Less than 5</b>
<b>100,000</b>	<b>Less than 25</b>

- ◆ What appears to be clean room air can have millions of particles per cubic foot.

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## Sterile Products – Basic Operations - Classified Environments

- ◆ Colony Forming Units
- ◆ Microorganisms controlled through cleaning procedures and gowning



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## Sterile Products – Basic Operations - Classified Environments

- ◆ HEPA Filters to control particulates

(High Efficiency Particulate Air) Filter




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## Sterile Products – Basic Operations - Formulation

- ◆ Class 100,000 or Class 10,000 area, depending upon product. Note: at this point the product has not been sterilized.

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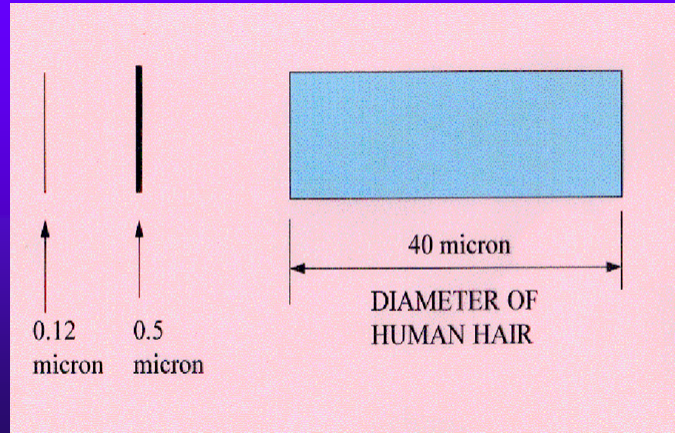


## Sterile Products – Basic Operations - Product Sterilization

- ◆ Filtration through a 0.2 micron sterilizing filter
- ◆ Terminal sterilization (after the product is in its final container) by heating to approximately 121 degrees C (250 degrees F). in an autoclave.

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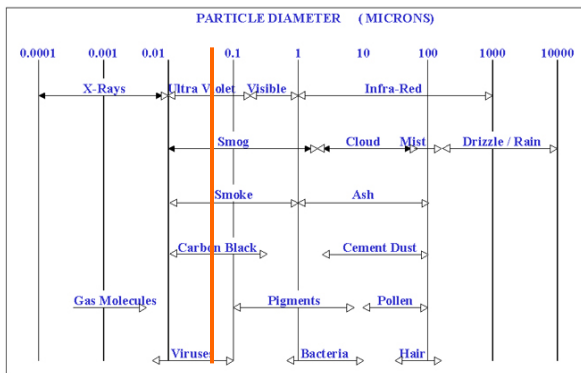
## Sterile Products – Basic Operations – Particle Size



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## Sterile Products – Basic Operations – Contaminants

### COMMON AIR CONTAMINANTS



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## Sterile Products – Basic Operations - Filling

- ◆ Class 100 Area
- ◆ Seamless Floors
- ◆ Impact resistant smooth wall finish
- ◆ Continuous Seamless Ceiling/HEPA Ceiling
- ◆ Coved corners
  - Wall to wall
  - Wall to floor
  - Wall to ceiling

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## Sterile Products – Basic Operations – Wall/Floor Details

- ◆ Class 100 and Class 10,000 Areas



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## Sterile Products – Basic Operations - Cleanroom

- ◆ Primary source of contamination is people



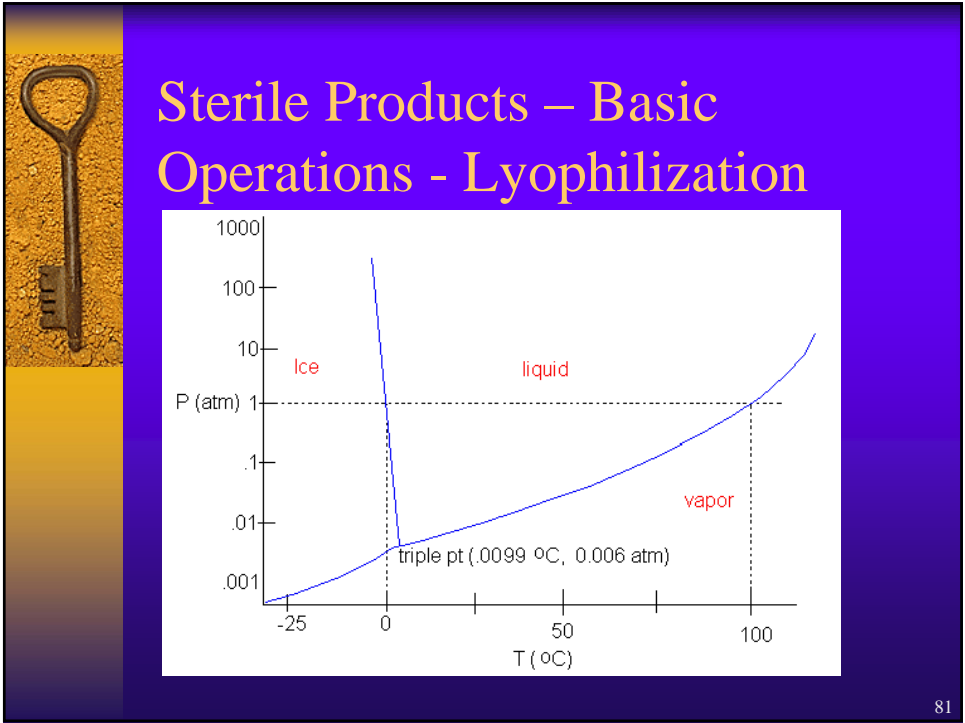
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## Sterile Products – Basic Operations – Laminar Flow Unit



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## Sterile Products – Basic Operations - Packaging

- ◆ Similar to packing for non-sterile liquid products except that vial sizes are much smaller than those for orally administered liquids.

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## Summary:

- ◆ Equipment utilized for the manufacture of tablets, orally administered liquids, sterile vials, and sterile freeze dried vials.
- ◆ Facilities for non-sterile products
- ◆ Facilities for sterile products
- ◆ Laminar Flow to control particles and microorganisms
- ◆ Why Lyophilization (Freeze Drying) is used and why it works

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**Questions & Discussion**

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