Parenteral technology

PDA
Parenteral Drug Association

Parenteral Drug Association

Connecting People, Science and Regulation

Parenteral Preparations

- Introduction and definitions
- Advantages and limitations
- Routes of parenteral administration
- Classifications of injections
- Specifications and requirements
- Components of parenteral products
- Sterilization methods
- Production process
- Compendial quality control testing
- Quality assurance

Parenteral Preparations

Definitions Background

- **para**: outside
- **enteron**: intestine
- These are the preparations which are given other than oral routes.

Parenteral Preparations

Definitions Background

- **B.P.: "Parenteral** preparations are **sterile** preparations intended for administration by injection, infusion or implantation into human or animal bodies"

WHO: Parenteral preparations are **sterile, pyrogen-free** liquids (solutions, emulsions, or suspensions) or solid dosage forms containing one or more active ingredients, packaged in either single-dose or multidose containers. They are intended for administration by injection, infusion, or implantation into the body.

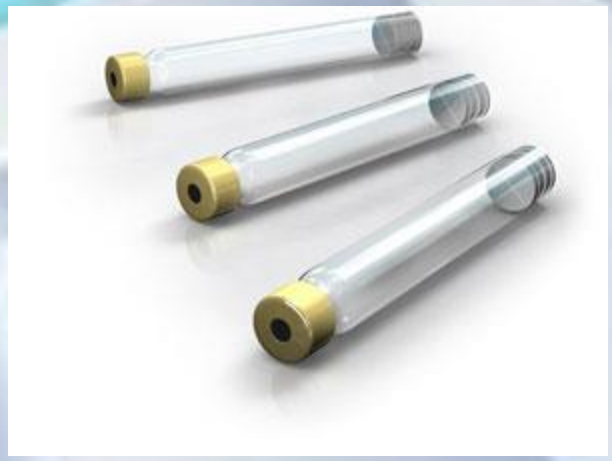
USP 24/NF19

- **Parenteral** preparations "preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are administered using gravity or force directly into a blood vessel, organ, tissue
- Parenteral products are prepared carefully by methods designed to ensure that they meet pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of growth of microorganisms.

Parenteral Preparations

Definitions Background

- An Injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration.

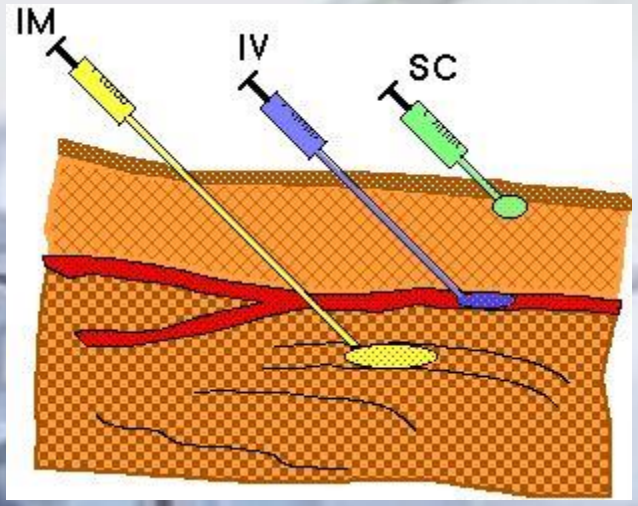


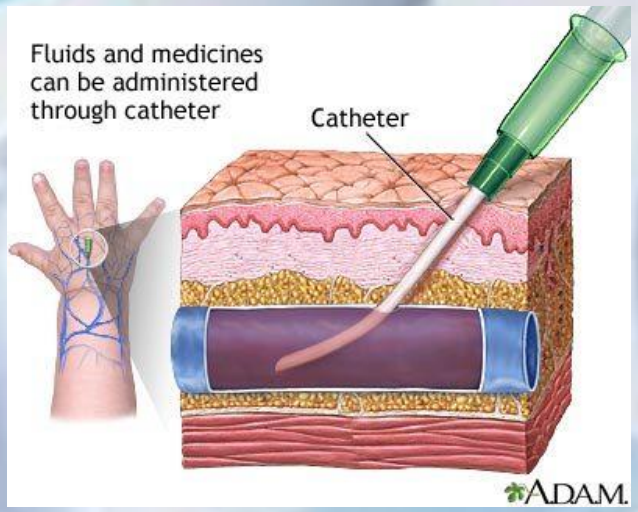
Parenteral Preparations

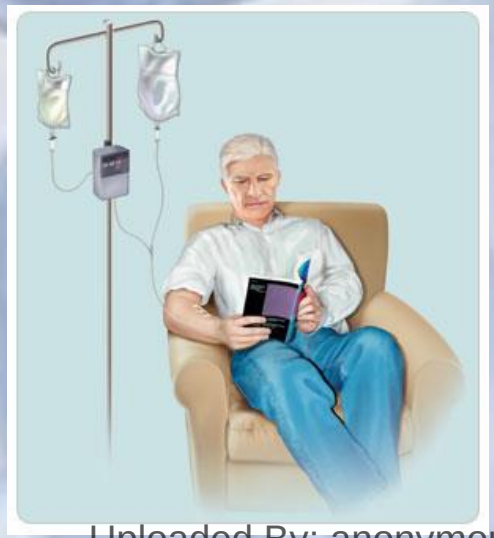
Definitions Background

IV Injection involves administration of Small volume parentrals (SVP) medications by a syringe into the a vein directly to blood stream

IV infusion involves administration of Large volume parentrals LVP via a catheter into the vein directly to blood stream







Parenteral Preparations

Definitions Background

large-volume parenterals(LVP)

- Sterile preparations intended for parenteral application with a volume of 100ml or more in one container of the finished dosage form.

Small volume parenterals (SMP)

- Sterile preparations intended for parenteral application with a volume less than 100ml

Parenteral Preparations

Definitions Background

contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

Parenteral Preparations

Definitions Background

Cross contamination

"Contamination of a starting material, intermediate product, or finished product with another starting material or product during production."(WHO)

Parenteral Preparations

Definitions Background

Sources of product contamination

- **People (most common)**

–Touch contamination

–Generation of particulates from shedding cells or hair

- **Air Supply**

–Heating, Ventilation and Air Conditioning (HVAC)

- **Infiltration**

–Particles from adjacent spaces (e.g. entrance, hall)

- **Internal generation**

–Walls, floors,ceilings, packaging, equipment

Parenteral Preparations

Definitions Background

Sterility

The complete destruction of all living organisms and their spores or their complete removal from the formulation.

All parenterals,as well as otic, nasal, ophthalmic solutions, must be sterile, including primary packaging materials

Parenteral Preparations

Definitions Background

- *Aseptic processing and packaging* means the filling of a commercially sterilized cooled product into presterilized containers, followed by aseptic hermetical sealing, with a presterilized closure, in an atmosphere free of microorganisms AND atmospheric particles is limited .

Parenteral Preparations

Definitions Background

- **PYROGEN** : **Any substance or agent** causes a rise in body temperature or induces a fever

- **Endotoxins** are part of the outer membrane of the cell wall of Gram-negative bacteria.

Endotoxins are complex lipopolysaccharides (LPS), major cell wall components in all Gram-negative bacteria.

Parenteral Preparations

Why Parenteral?

1) Rapid action
2) Oral route can not be used
3) Not effective except as injection
4) Many new drugs: *Biotechnological Drugs* can only be given by parenteral
5) New drugs require to maintain potency so that they are given by parenteral.

Parenteral Preparations

Advantages:

- Quick onset of action
- Suitable for the drugs which are not administered by oral route
- Useful for unconscious or vomiting patients.
- Duration of action can be prolonged by modifying formulation.
- Suitable for nutritive like glucose & electrolyte.
- Suitable for the drugs which are inactivated in GI fluid

Parenteral Preparations

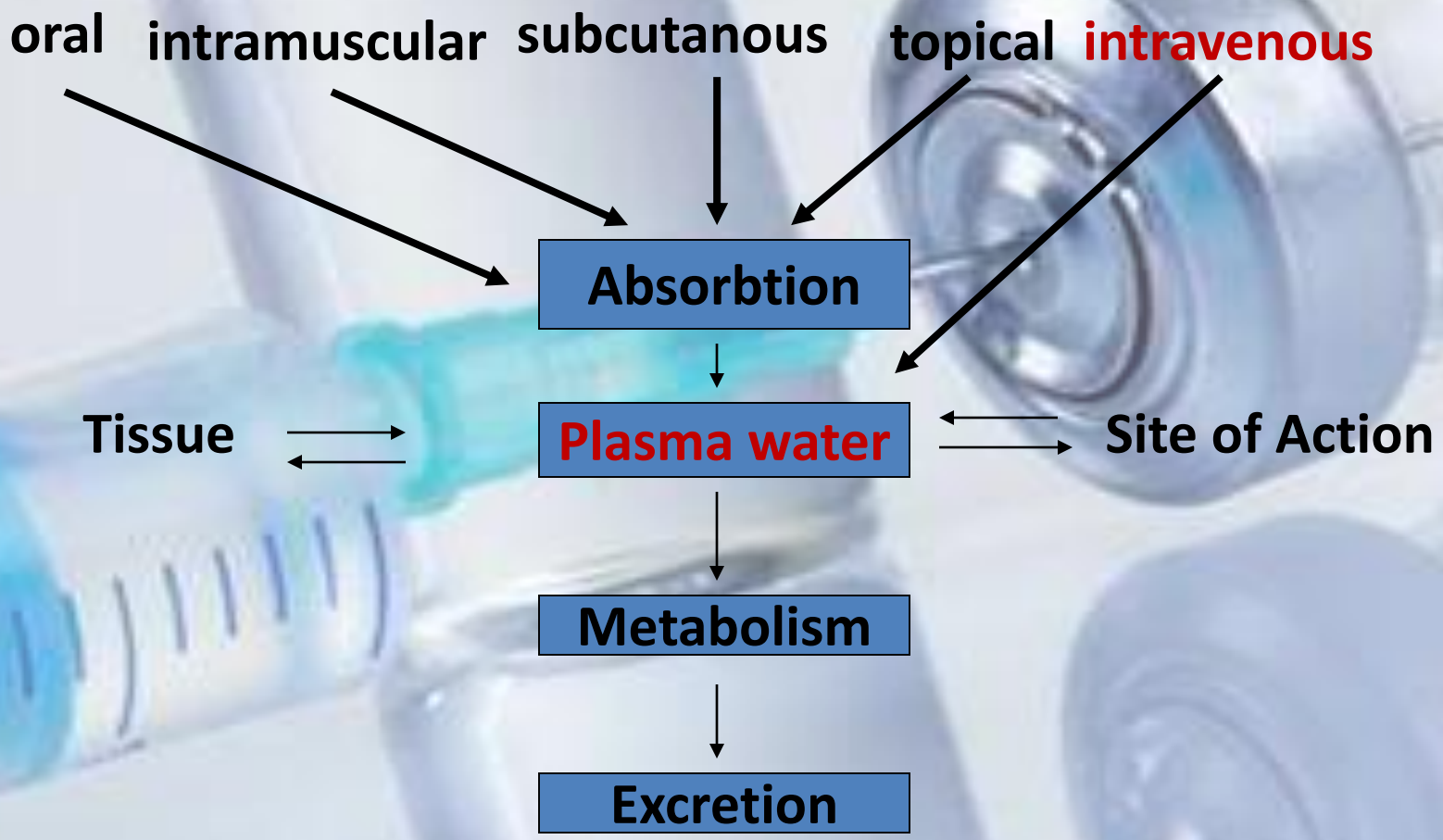
Disadvantages

- Injections may cause pain at the site of injection
- Only trained person is required
- Requires strict control of sterility & non pyrogenicity than other formulation

(Mistakes)

- If given by wrong route, difficult to control adverse effect
- Difficult to save patient if overdose
- Once injected cannot be controlled (retreat)
- Sensitivity or allergic reaction at the site of injection

Drug Administration



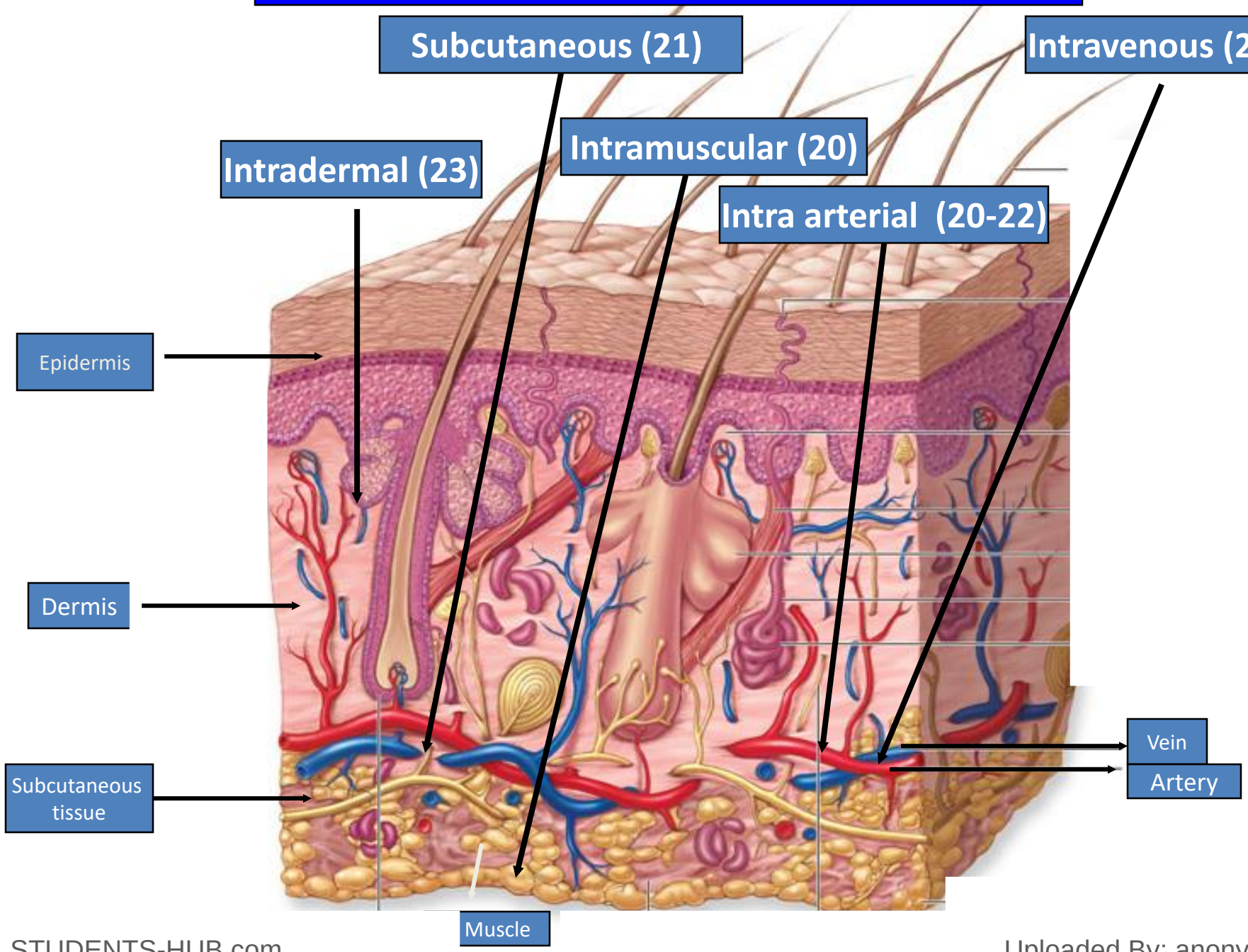
Parenteral Preparations

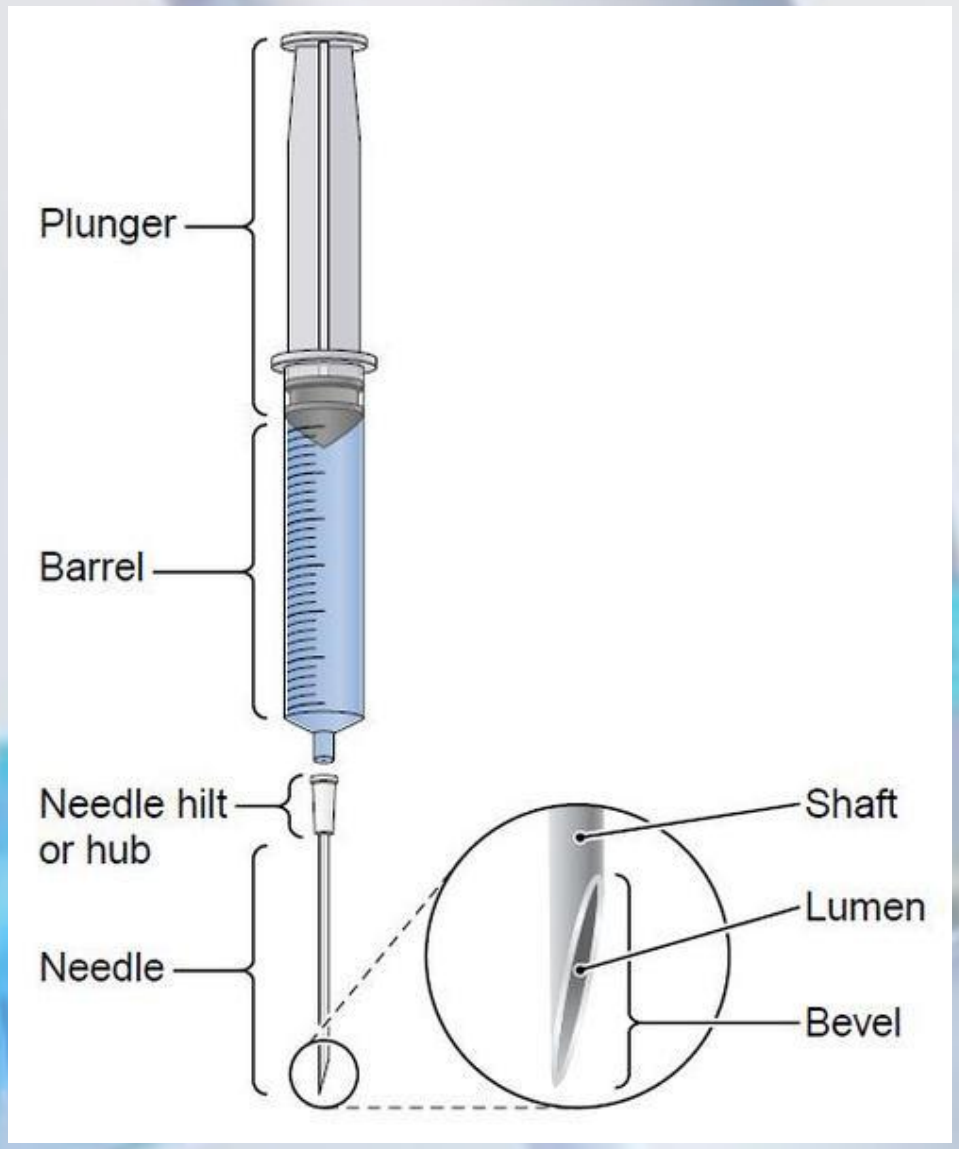
Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:

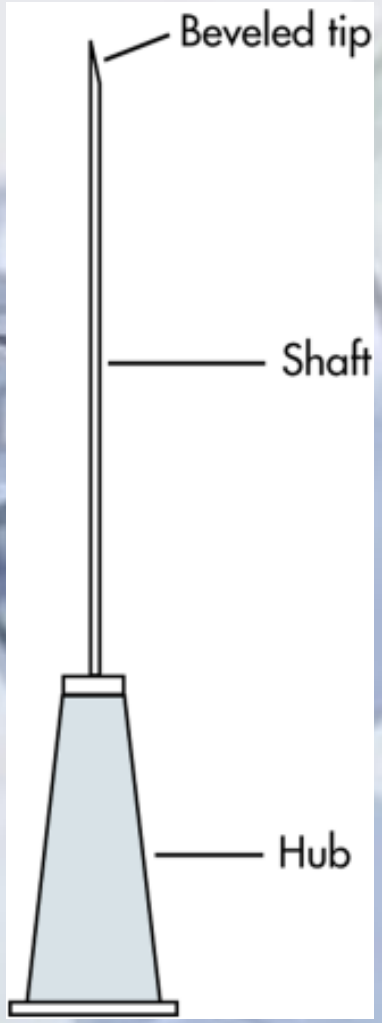
Requirements for Parenteral preparations

- All products **must** be sterile.
- All products **must** be free (**LIMITED**) from pyrogenic (endotoxin) contamination.
- Injectable solutions **must** be free from visible particulate matter.
- Products **should** be isotonic
- All products **must** be stable
- Products **must** be compatible,
- APIs & Other Pharma Ingredients used **must** meet special purity and other standards.
- Specific and high quality packaging

Routes of Parenteral Administration







(From Clayton, B.D., Stock, Y.N. [2004]. *Basic pharmacology for nurses.* [13th ed.]. St. Louis: Mosby.)

Parts of a needle.

GAUGE	18G	19G	20G	21G	22G	23G	24G	25G	26G	27G
O.D. (mm)	1.25	1.08	0.9	0.81	0.71	0.64	0.56	0.51	0.45	0.41
WING COLOR	Pink	Light Yellow	Yellow	Dark Green	Black	Dark Blue	Purple	Orange	Brown	Gray

I.D. (inner diameter) *O.D. (outer diameter)*

color	gage	ID size in	ID size mm	OD size in	OD size mm
olive	14	0.060	1.55	0.072	1.83
amber	15	0.054	1.37	0.065	1.65
grey	16	0.047	1.19	n/a	n/a
green	18	0.033	0.84	0.050	1.27
pink	20	0.023	0.61	0.036	0.91
purple	21	0.020	0.51	0.032	0.81
blue	22	0.016	0.41	0.028	0.71
orange	23	0.013	0.33	0.025	0.64
red	25	0.010	0.25	0.020	0.51
clear	27	0.008	0.20	0.016	0.41
lavender	30	0.006	0.15	0.012	0.30
yellow	32	0.004	0.10	0.009	0.23

Please note: OD dimensions are for stainless steel tips only.

Parenteral Administration

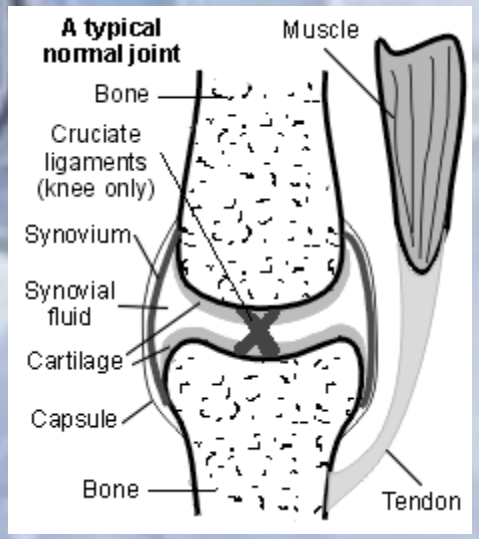
- Needles
  - Parts are the hub, shaft, and beveled tip.
  - Size of the diameter of the inside of the needle's shaft determines the gauge of the needle; the smaller the gauge, the larger is the diameter.
  - Needle gauge selection is based on the viscosity of the medication.
- Needle Length
  - Selected based on the depth of the tissue into which the medication is to be injected

Parenteral Preparations

Parental Routes of Administration

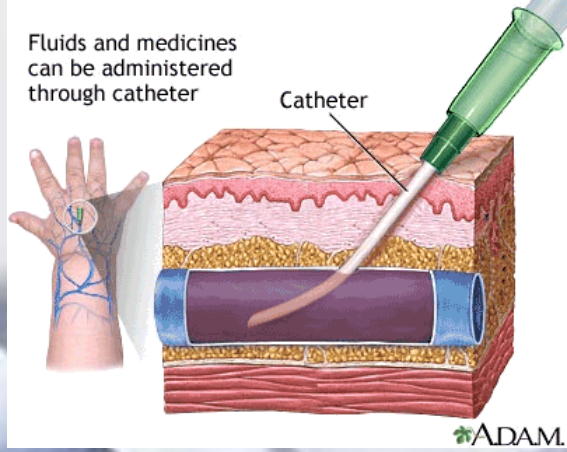
Most Common: 1. Subcutaneous (**SC; SQ ;Sub Q)**
2. Intramuscular (IM)
3. Intravenous (IV)
4. Intradermal ID (*intracutaneous)*

Others: 5. Intra-articular
6. Intrasynovial
7. Intraspinal
8. Intrathecal
9. Intra-arterial (IA)
10. Intrapleural
11. Intracardial
12. Intra-abdominal injection



Parental Routes of Administration

Intravenous (IV)



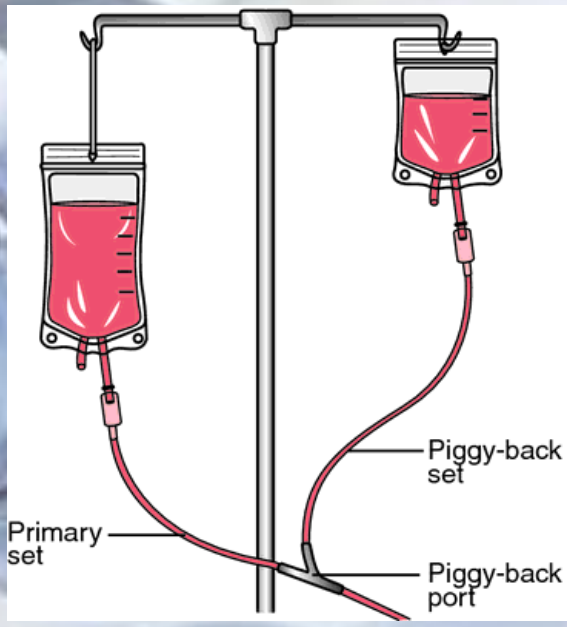
- Into the vein
- 1 to 1000 ml
- rate 1ml/ 10 sec. for volume up to 5 ml & 1 ml/ 20 sec. for volume more than 5 ml.

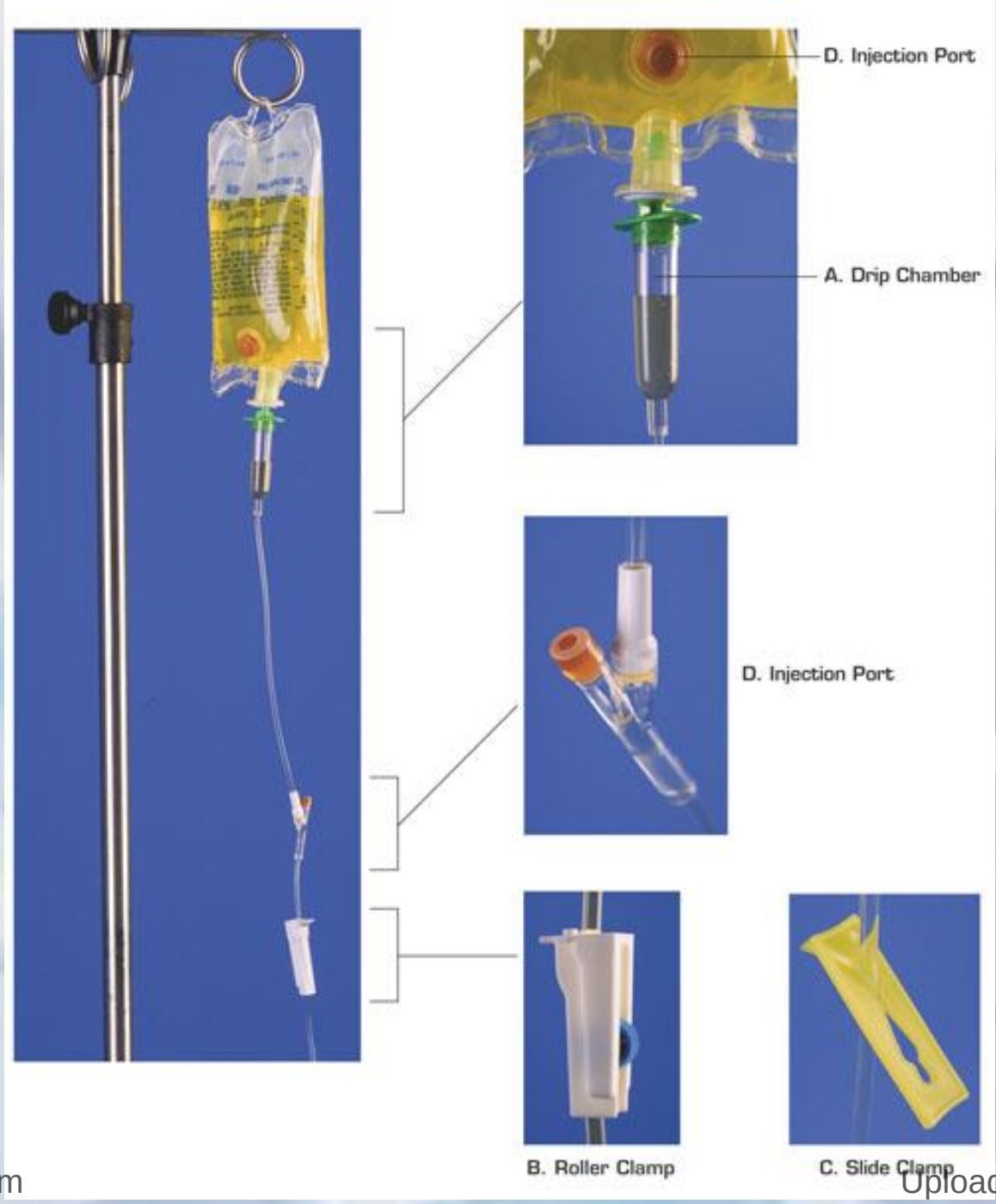
Given:

- Aqueous solutions
- Hydro alcoholic solutions
- Emulsions
- Liposome
- Must mixed with the blood
- Not precipitate

Parental Routes of Administration
Intravenous (IV)

- IV infusion of large volume fluids (100-1000 ml)
- This is used to supply electrolytes & nutrients to restore blood volume & to prevent tissue dehydration.
- Combination of parenteral dosage forms for administration as a unit product is known as an IV admixture.
  - Lactated Ringer Injection USP
  - NaCl Injection USP (0.9 %)– (replenish fluid & electrolyte)
  - Dextrose Injection USP (fluid & electrolyte)

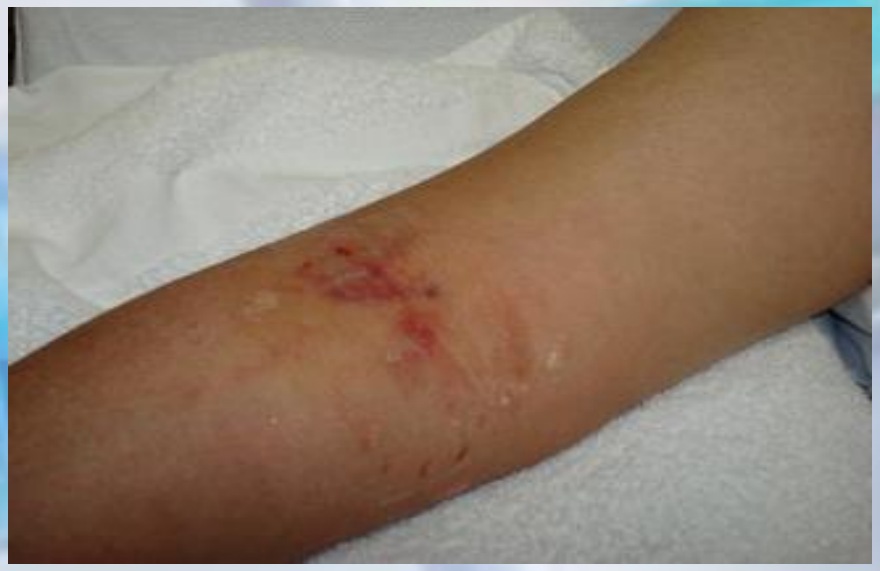




Precautions IV

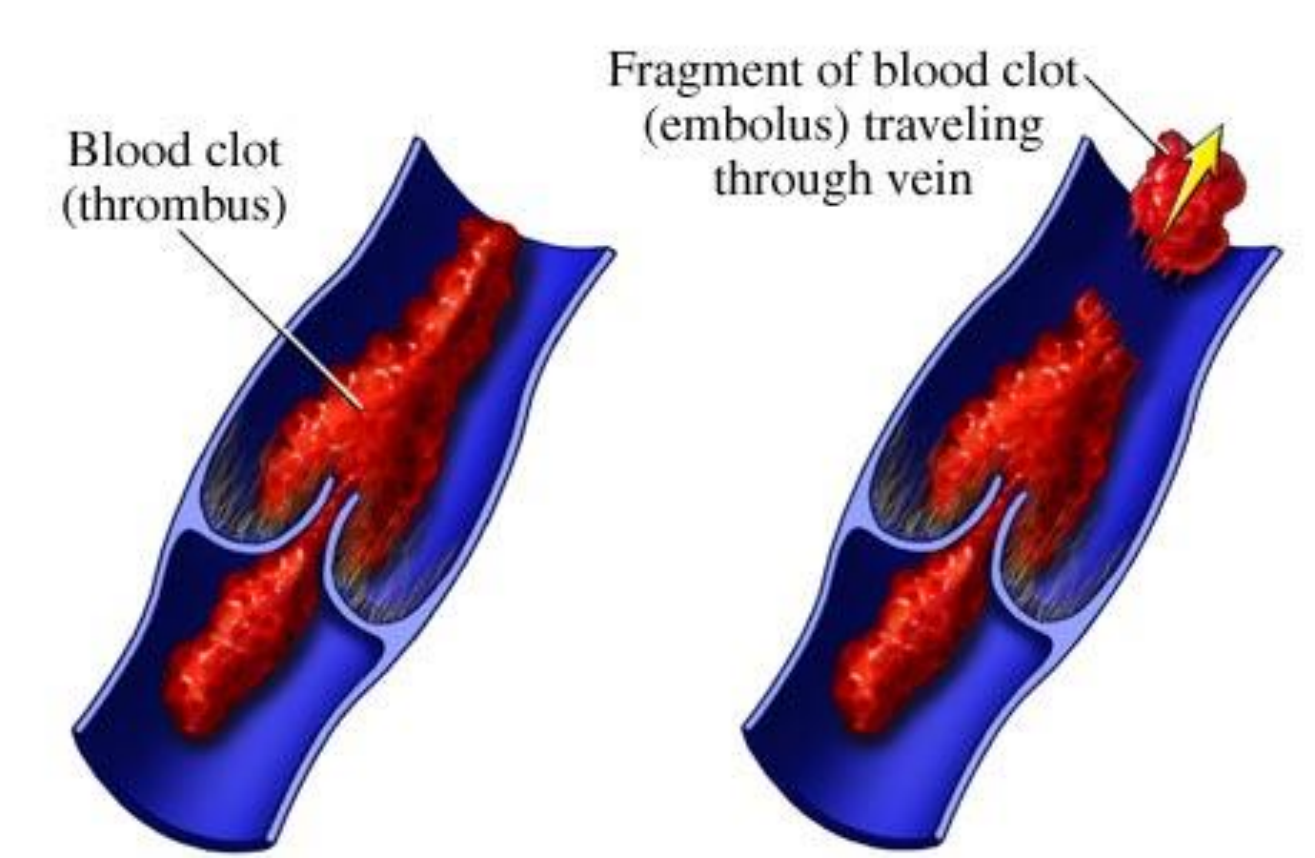
Infiltration

- Breakdown or collapse of veins that allows the drug to leak into sites surrounding site of needle causing edema and tissue damage.



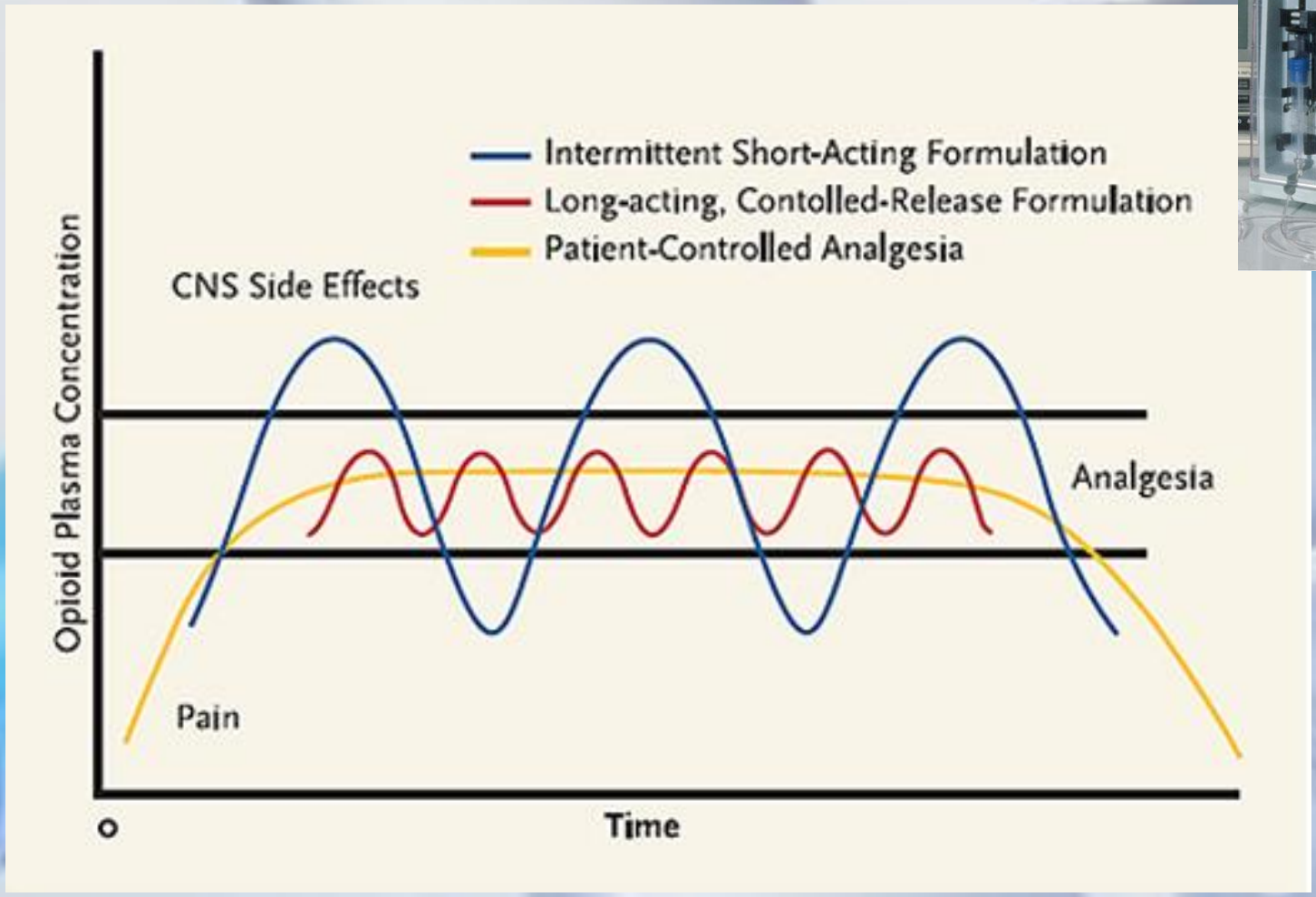
Parental Routes of Administration Intravenous (IV)

Precautions IV



Parental Routes of Administration Intravenous (IV)

Patient-controlled analgesia (PCA)



constant rate infusion and /or demand dosing

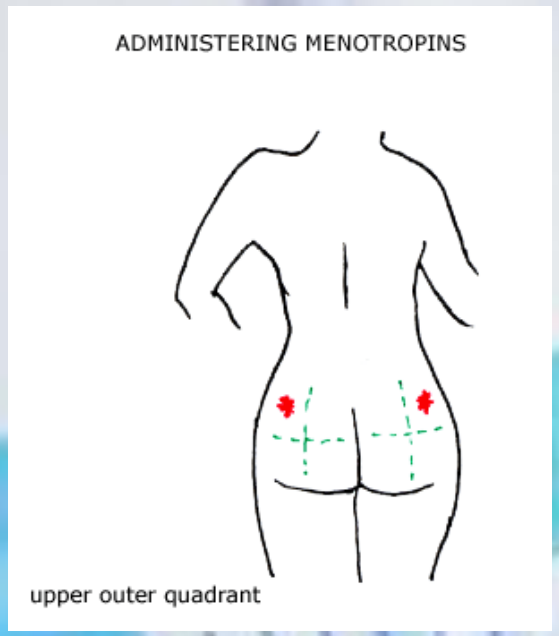
- https://www.youtube.com/watch?v=NJIZTk89PH8
- https://www.youtube.com/watch?v=QOz4Hbkg2iw

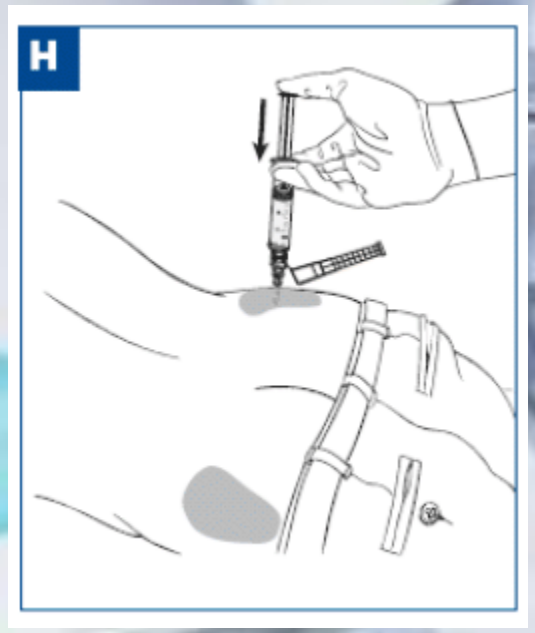
Parental Routes of Administration

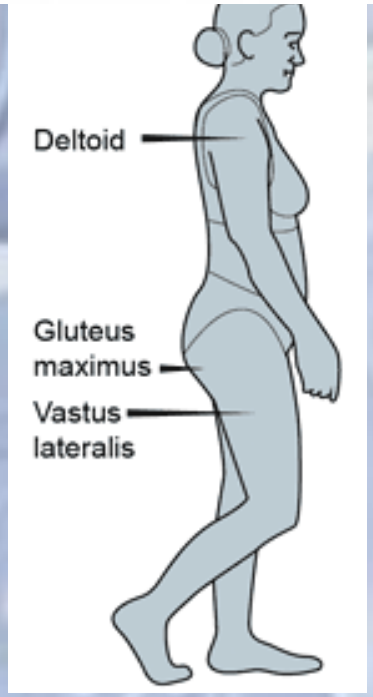
Intramuscular (IM):

Principle sites:

- Gluteal (buttocks)
- Deltoid (upper arms)
- Vastus lateralis (lateral thigh)







Parental Routes of Administration

Intramuscular (IM):

- Given:
  - Solutions
  - Emulsions
  - Oils
  - Suspension

Slower onset of action compared to IV.
Longer duration (depot effect)
Muscles are highly vascular = rapid absorption about 10-30 min(aq. Sol.)
Suspension and oil-based injections (slowly dissolved, slowly absorbed)
More practical for use outside the hospital compared to IV injections
Volume of injection up to 5 ml.

Need to be isotonic

Striated muscle fibre
0.5 to 2 ml sometimes upto 5 ml
2 to 3 inch & 20 to 22 gauge needle is used

Parental Routes of Administration

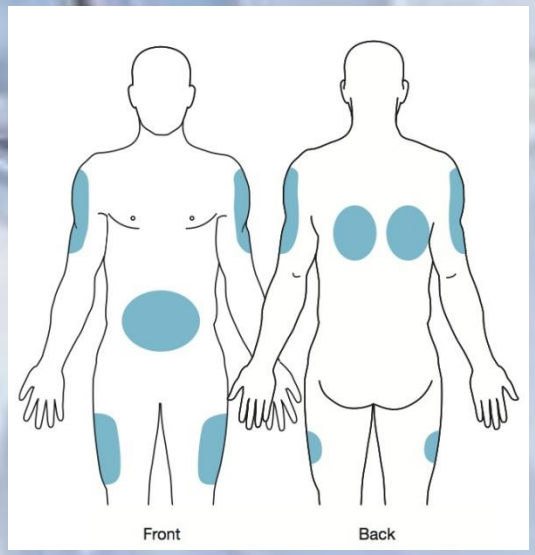
Subcutaneous (SC; SQ ;Sub Q)

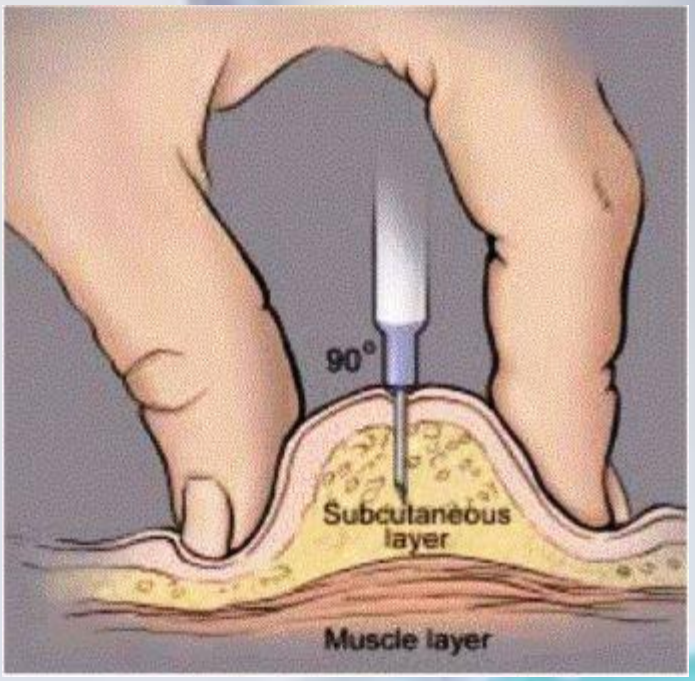
- The injection is given under the skin
- Need to be isotonic
- Upto 2 ml is given
- Using ½ to 1 inch 24-26 gauge needle or smaller needle

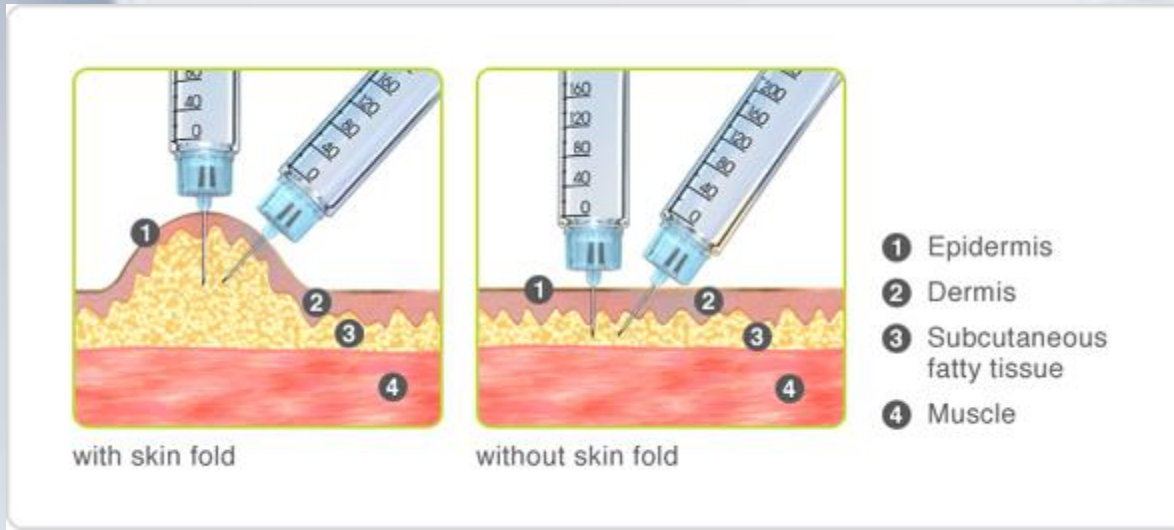
- **Given:**

  solution ,suspension , emulsion,oil

  - Vaccines
  - Insulin







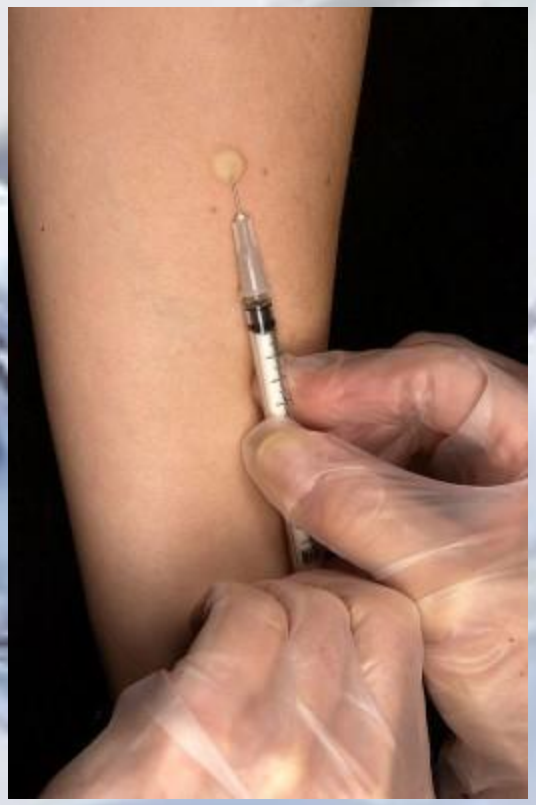
The rate of absorption is slower than the IV, IM route
subcutaneous administration is generally more rapid and predictable than after oral administration

There are several ways to change the absorption rate:
use heat or massage the site to increase the absorption rates of many drugs.
co-administer vasodilators to increase absorption rates of some drugs. Conversely, epinephrine decreases blood flow which can decrease the absorption rate.

Parental Routes of Administration

Intradermal ID

- Also called as diagnostic testing
- 0.1ml
- ½ inch, 23 to 26 gauge needle
- Should be isotonic

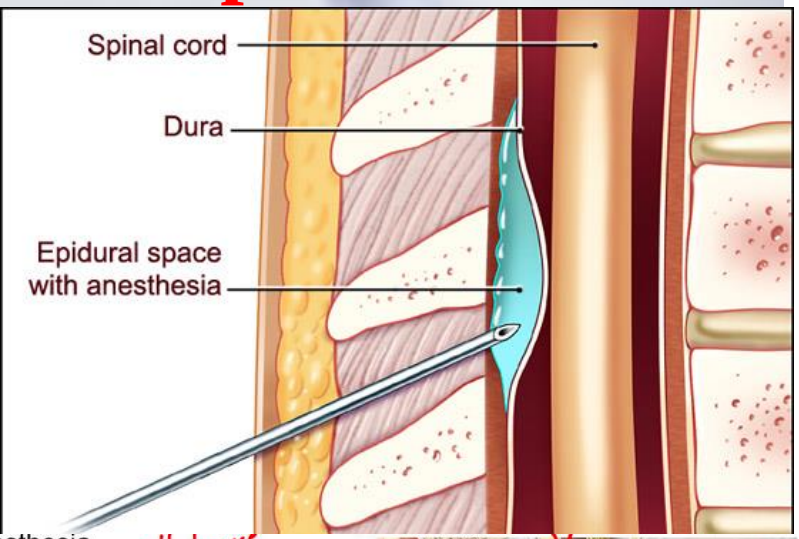


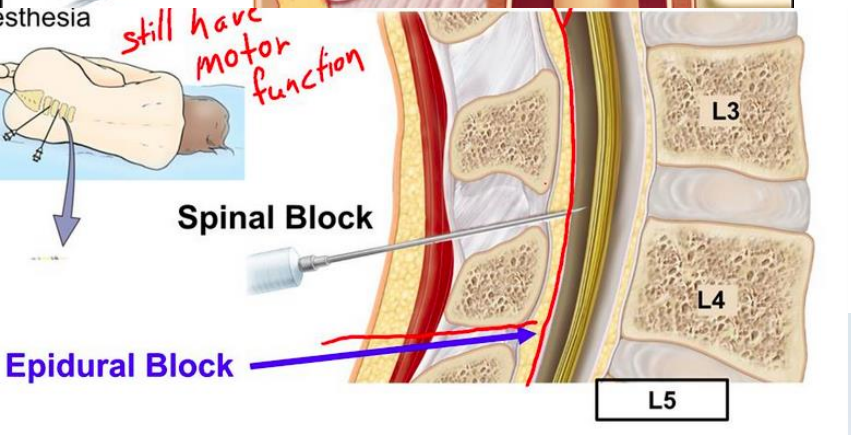
- Given:
  - Diagnostic agents
  - Immunization
  - Desensitization

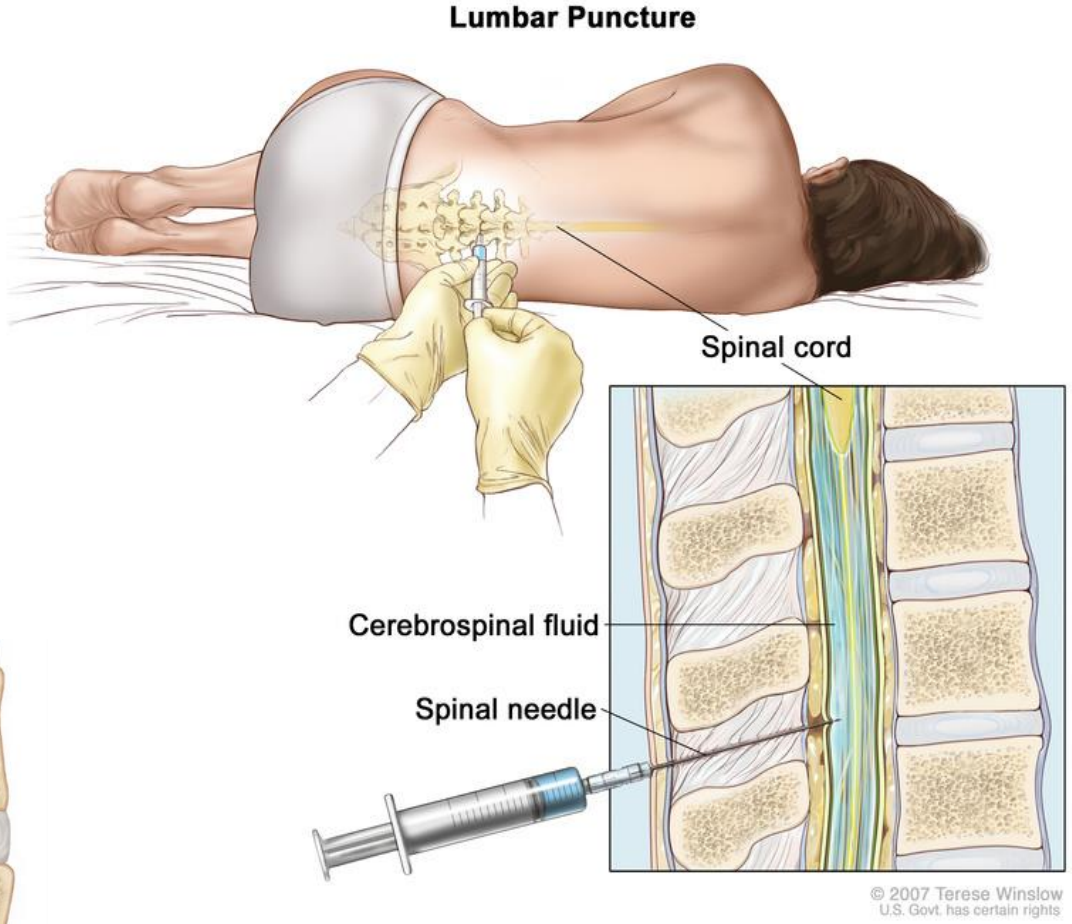
Intraspinal

Intrathecal

Epidural





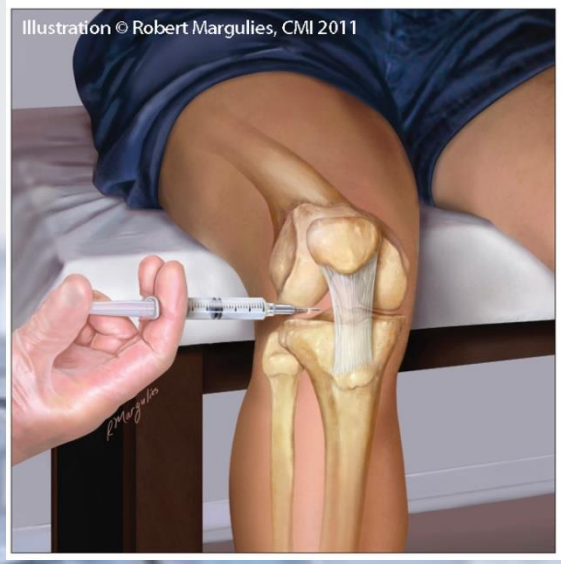


useful in spinal anaesthesia, chemotherapy, or pain management applications.

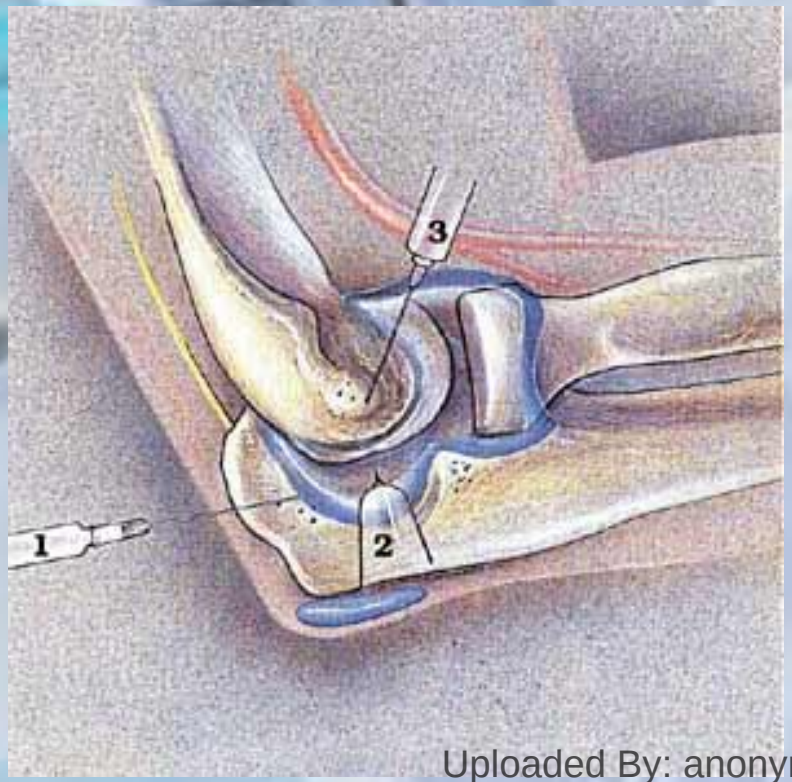
Intraarticular

– Given directly into the joints

- Given:
  - Morphine
  - Steroids
  - NSAID's
  - Antibiotics

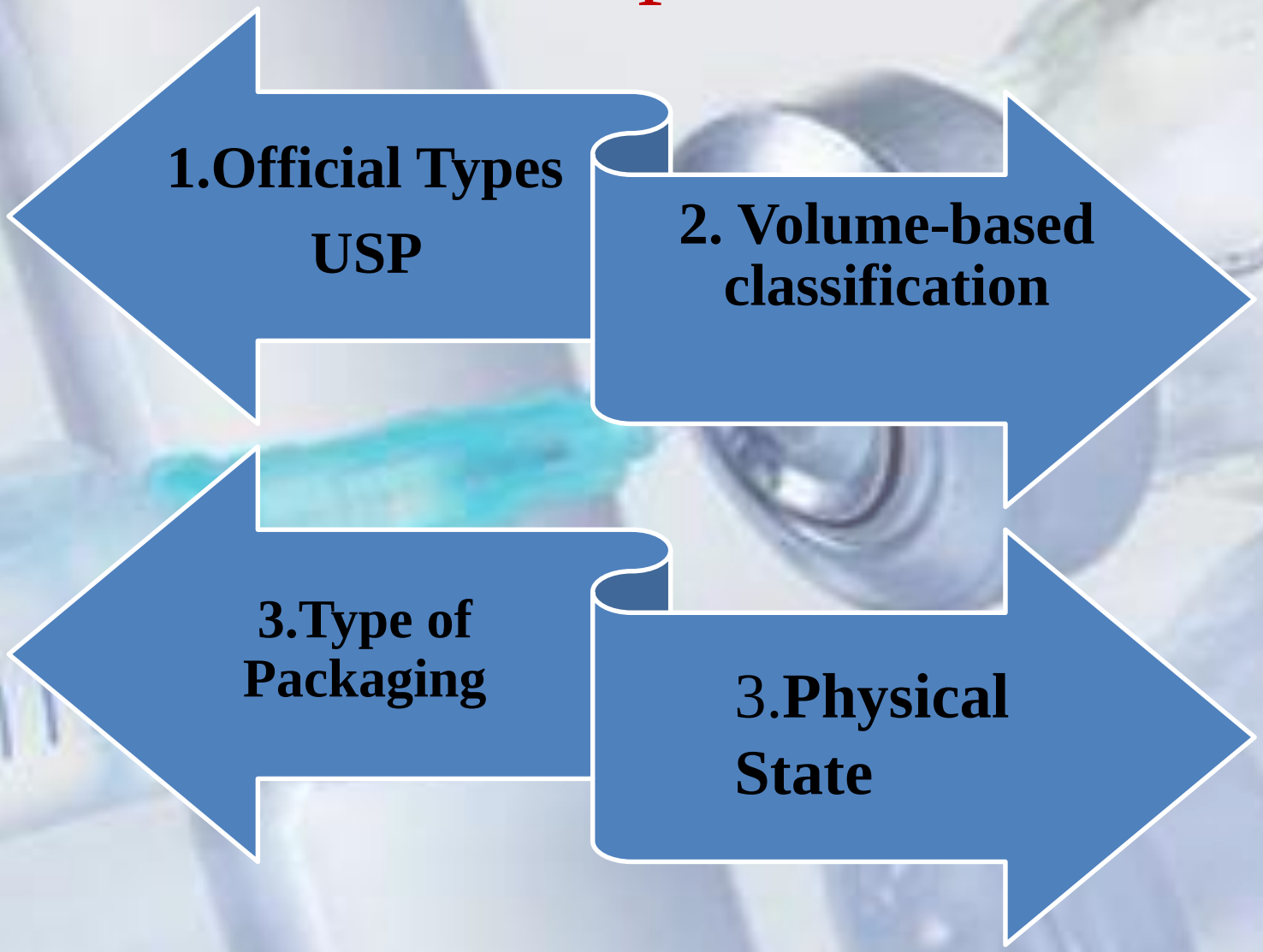


Intrasynovial



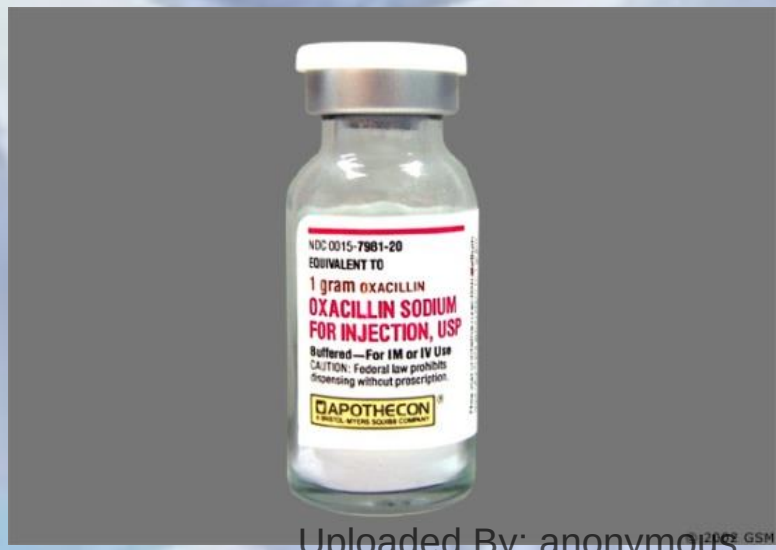
- Intra-arterial (IA):
  - Direct into the artery
  - 2 to 20 ml
  - 20 to 22 gauge
  - Solutions & emulsions can be administered
- Given:
  - Radio opaque media
  - Antineoplastic
  - Antibiotics

Classification of parenterals



Official Types of Injections

1. Injection
2. For injection .
3. Injectable emulsion
4. Injectable suspension
5. For injectable suspension



Types of Parenteral Preparation

1. Type of Packaging

1-Single dose units (ampoules, pre-filled syringes)

2-Infusion solution

3-Multiple dose units (vials)

2. Volume

1-Small volume parenterals (SMP) of less than 100 ml.

2-Large volume parenterals (LVP) of 100 ml or more

Types of Parenteral Preparation

3.**Physical State**

1-Sterile Solutions

2-Sterile Suspensions

3-Sterile Emulsions

4-Sterile Solid

The solutions and suspensions of drugs intended for injection are prepared in the same general manner as solutions and disperse systems with the some differences

Formulation of Parenteral

Formulation of Parenteral

1. Therapeutic agents
2. Vehicles
   i. Water
   ii. Water miscible vehicles
   iii. Non- aqueous vehicles
3. Added substances (Additives)
   i. Antimicrobials
   ii. Antioxidants
   iii. Buffers
   iv. Bulking agents
   v. Chelating agents
   vi. Protectants
   vii. Solubilizing agents
   viii. Surfactants
   ix. Tonicity- adjusting agents

Formulation of Parenteral

During the formulation of parenteral products, the following factors are critical:

(a) The vehicle in which the drug is dissolved or dispersed

(b) Volume (dose) of the injection

(c) Adjustment to isotonicity

(d) Adjustment of pH

(e) Stabilisers

(f) Preservatives

(h) Concentration units

Formulation of Parenteral

1.Therapeutic ingredients:

- Insulin
- Antibiotics
- Anticancer
- Steroids
- Vaccines
- Antipyretic
- Analgesics
- Anti- inflammatory
- LVP’s like Dextrose, NaCl or combination etc….

Formulation of Parenteral

SOLVENTS AND VEHICLES FOR INJECTIONS

2.Solvents:

- Water
  - Should meet compendial requirements
- Water miscible vehicles
  - Ethyl alcohol
  - PEG
  - PG
- Non aqueous vehicles
  - Fixed oils

Formulation of Parenteral

Aqueous solvents

- Water for Injection (WFI).
- Sterile Water for Injection (SWFI).
- Bacteriostatic Water for Injection (BWFI).
- Sodium chloride injection (USP)
- Bacteriostatic sodium chloride injection
- Sterile Water for Inhalation.
- Sterile Water for Irrigation

Formulation of Parenteral

Water for Injection (WFI).

- It is the water intended to be used in the manufacture of injectable products, which are to be sterilized after their preparation.
- not required to be sterile, it should be **free (limited) from pyrogens**.
- The total number of dissolved solids must not exceed 10 ppm
- it is used within 24 hrs of its collection, WFI should be discarded or maintained sterile or stored in tight containers at:
- **5.0 ºC for small volumes**
- **80.0 ºC for larger tanks**

Formulation of Parenteral

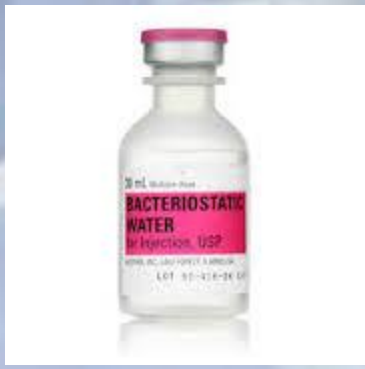
Sterile Water for Injection (SWFI).

- Sterile Water for Injection (USP) is a sterile, non-pyrogenic preparation of water for injection which contains no antimicrobial agent or added buffer and is supplied only in single-dose containers.
- **Uses: used to dilute or dissolve already-sterilized and packaged injectable medications such as the dry powders of Na phenobarbitol & Ampicillin Na.**
- It is added under aseptic conditions.
- It must be pyrogen-free.
- Doesn't contain antimicrobial agent.
- **It must be isotonic when intended for Intra-vascular**

Formulation of Parenteral

Bacteriostatic Water for Injection (BWFI)

- a sterile, nonpyrogenic preparation of water for injection containing 0.9% (9 mg/mL) of benzyl alcohol added as a preservative.
- It is supplied in a multiple-dose container from which repeated withdrawals may be made to dilute or dissolve drugs for injection.
- The pH is 5.7 (4.5 to 7.0).
- **If the patient will receive more than 5mL of parenteral preparation, BWFI is NOT the vehicle of choice. Why?**
- should be compatible (doesn't interact) with the drug



Formulation of Parenteral

Sodium chloride injection USP

- Is a sterile isotonic solution of NaCl in water for injection.(154 mEq)
- Contains no antimicrobial agent.
- May be used as a sterile vehicle in solutions or suspensions of drugs for parenteral administration.

Formulation of Parenteral

Bacteriostatic sodium chloride injection

- This preparation is designed for parenteral **use only after addition of drugs that require dilution or must be dissolved in an aqueous vehicle prior to injection**.

- Bacteriostatic 0.9% Sodium Chloride Injection, USP is a **sterile, non pyrogenic, isotonic solution** of sodium chloride in water for injection. Each milliliter (mL) contains sodium chloride 9 mg and 0.9% (9 mg/mL) benzyl alcohol added as a bacteriostatic preservative.

- May contain hydrochloric acid for pH adjustment. It is supplied in a multiple-dose container from which repeated withdrawals may be made to dilute or dissolve drugs for medication. **The pH is 5.0 (4.5 to 7.0).**
- Sodium Chloride, USP is chemically designated NaCl, a white crystalline powder freely soluble in water.

- .

Formulation of Parenteral

Non- aqueous vehicles

Solvents used must be????????

Considerations for selection solvents as vehicle for parenteral:

Viscosity, fluidity, Boiling point, vapor pressure, miscibility, purity, ease of purification and standardization

Water-miscible solvents **Can be given both IV , IM…….**

glycerin, polyethylene glycols, propylene glycol, alcohol, ethyl oleate, isopropyl myristate, and dimethyl acetamide.

vegetable oils,

The most commonly used fixed oils in injections are corn oil, cottonseed oil, peanut oil, and sesame oil. Castor oil and olive oil have been used on occasion

oil injections must not be administered intravenously

Formulation of Parenteral

ADDED SUBSTANCES

Formulation of Parenteral

ADDED SUBSTANCES

Preservatives

- Antimicrobial agents are added to multi-dose SVP
- Large volume parenterals (LVP) **must not** contain preservative
- Ideal preservative must be?????????

  - Ex..
    - Benzyl alcohol ------ 0.5 – 10 %
    - Benzethonium chloride -- 0.01 %
    - Methyl paraben ----0.01 – 0.18 %
    - Propyl paraben --- 0.005 – 0.035 %
    - Phenol --- 0.065 – 0.5 %

Formulation of Parenteral

ADDED SUBSTANCES

Antioxidants

- Used to protect product from oxidation
- Acts as reducing agent or prevents oxidation
- Ex:
  - **A) Reducing agent:**
    - » Ascorbic acid -- 0.02 – 0.1 %
    - » Sodium bisulphite-- 0.1 – 0.15 %
    - » Sodium metabisulphite-- 0.1 – 0.15 %
    - » Thiourea - 0.005 %
  - B) **Blocking agents**:
    - » Ascorbic acid esters- 0.01 – 0.015%
    - » BHT- 0.005 – 0.02 %
  - C) **Synergistic:**
    - » Ascorbic acid , Citric acid , Tartaric acid
  - D) **Chelating agent:**
    - » EDTA- 0.01- 0.075 %

Formulation of Parenteral

ADDED SUBSTANCES

Buffers

- Added to maintain pH,
- Change in pH may causes degradation of the products
- Acetates, citrates, phosphates are generally used.

- Factors affecting selection of buffers:
  - Effective range,
  - Concentration
  - Chemical effect on the total product
- The acceptable **pH range is 3-10.5 for IV preparations and 4-9 for other routes.**
- Buffers are included in injections to maintain the pH of the packaged product. However, the buffer used in the injection **must allow** the body fluids to change the product pH after injection.

- EXAMPLES:
  - HCl, NaOH, Acetic acid ,adipic acid, benzoic acid, citric acid, lactic acid

Formulation of Parenteral

ADDED SUBSTANCES

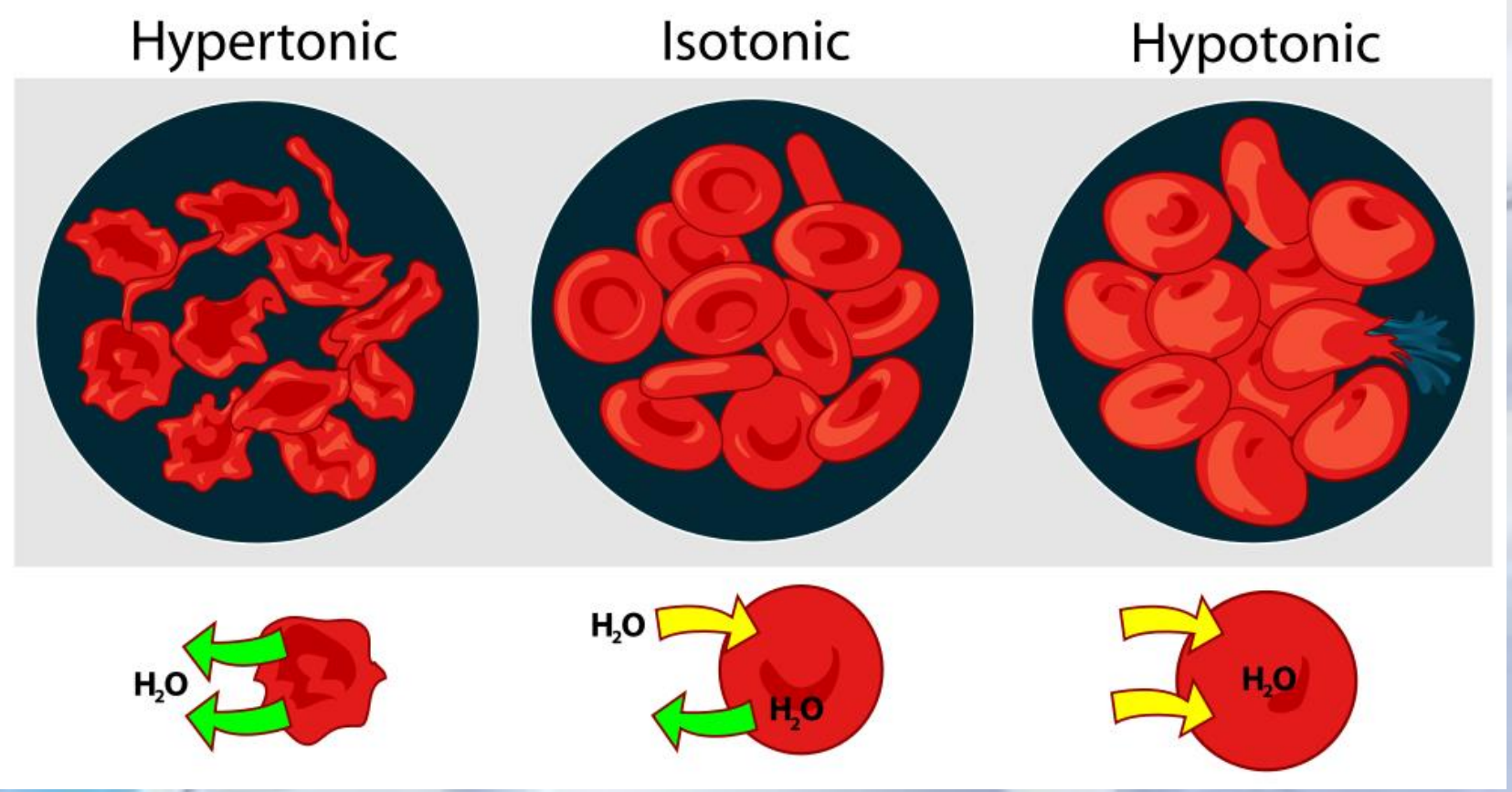
Tonicity-adjusting agents

- The osmotic pressure of blood is approximately **300 milliOsmoles/L** and ideally any sterile solution would be formulated to have the same osmolarity e.g., 0.9% w/v Sodium Chloride iv solution has an osmolarity of 308 mOsmole/L and 5% w/v Dextrose iv solution has an osmolarity of 280 mOsmol/L.
- Intravenous solutions that have larger osmolarity values (hypertonic) or smaller osmolarity values (hypotonic) may cause damage to red blood cells, pain, and tissue irritation.

Formulation of Parenteral

ADDED SUBSTANCES

Tonicity-adjusting agents



Sterilization

1. Moist heat sterilization (Steam)
2. Dry heat
3. Filtration
4. Gas
5. Ionizing radiation

finished product must pass sterility test.

Sterilization

- Sterilization is necessary for the **complete** destruction or removal of **all microorganisms** (including spore-forming and non-spore-forming bacteria, viruses, fungi, and protozoa) that could contaminate pharmaceuticals or other materials and thereby constitute a health hazard.
- Since the achievement of the absolute state of sterility cannot be demonstrated, the sterility of a pharmaceutical preparation can be defined only in terms of **probability**. The **efficacy** of any sterilization process will depend on the nature of the product, the extent and type of any contamination, and the conditions under which the final product has been prepared. The requirements for Good Manufacturing Practice should be observed throughout all stages of manufacture and sterilization.

Sterilization

1. Moist heat sterilization (Steam)
2. Dry heat
3. Filtration
4. Gas
5. Ionizing radiation

- **There are 3 different sterilization principles:**
  1. **Heat sterilization**
  2. **Chemical sterilization**
  3. **Radiation sterilization**

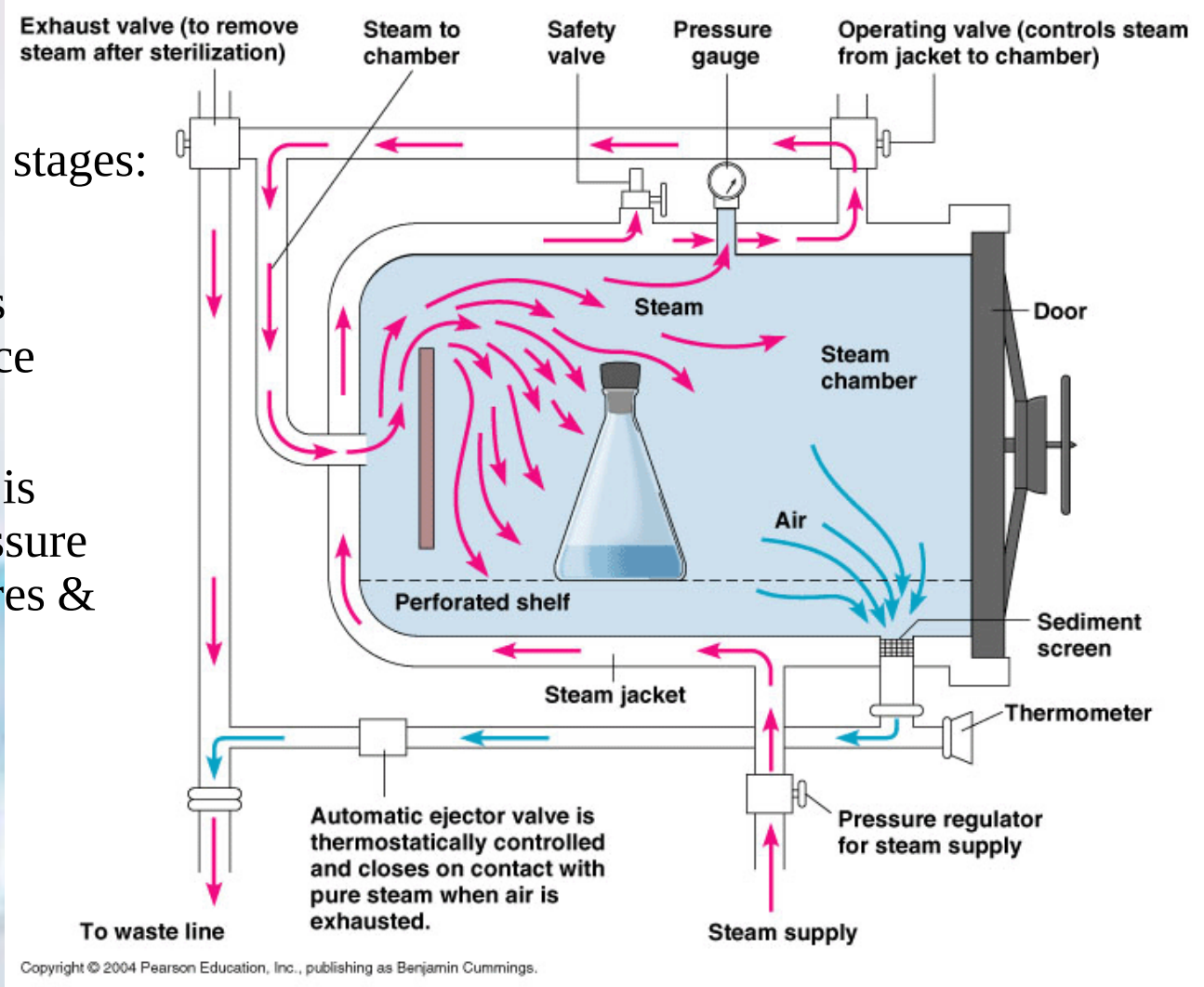
Moist heat sterilization (Steam)

Process is divided into 3 stages:

Pre-vacuum stage : air is withdrawn from device

Sterilizing stage : steam is introduced under pressure to specific temperatures & times.

Post-vacuum: steam is withdrawn to dry autoclave



Moist heat sterilization (Steam)

- **1. Steam sterilization**
- Method:Applying steam under high pressure
- Equipment:Autoclave (steam sterilizer)

Mechanism of microbial destruction:

denaturation and coagulation of some of organism's essential protein.

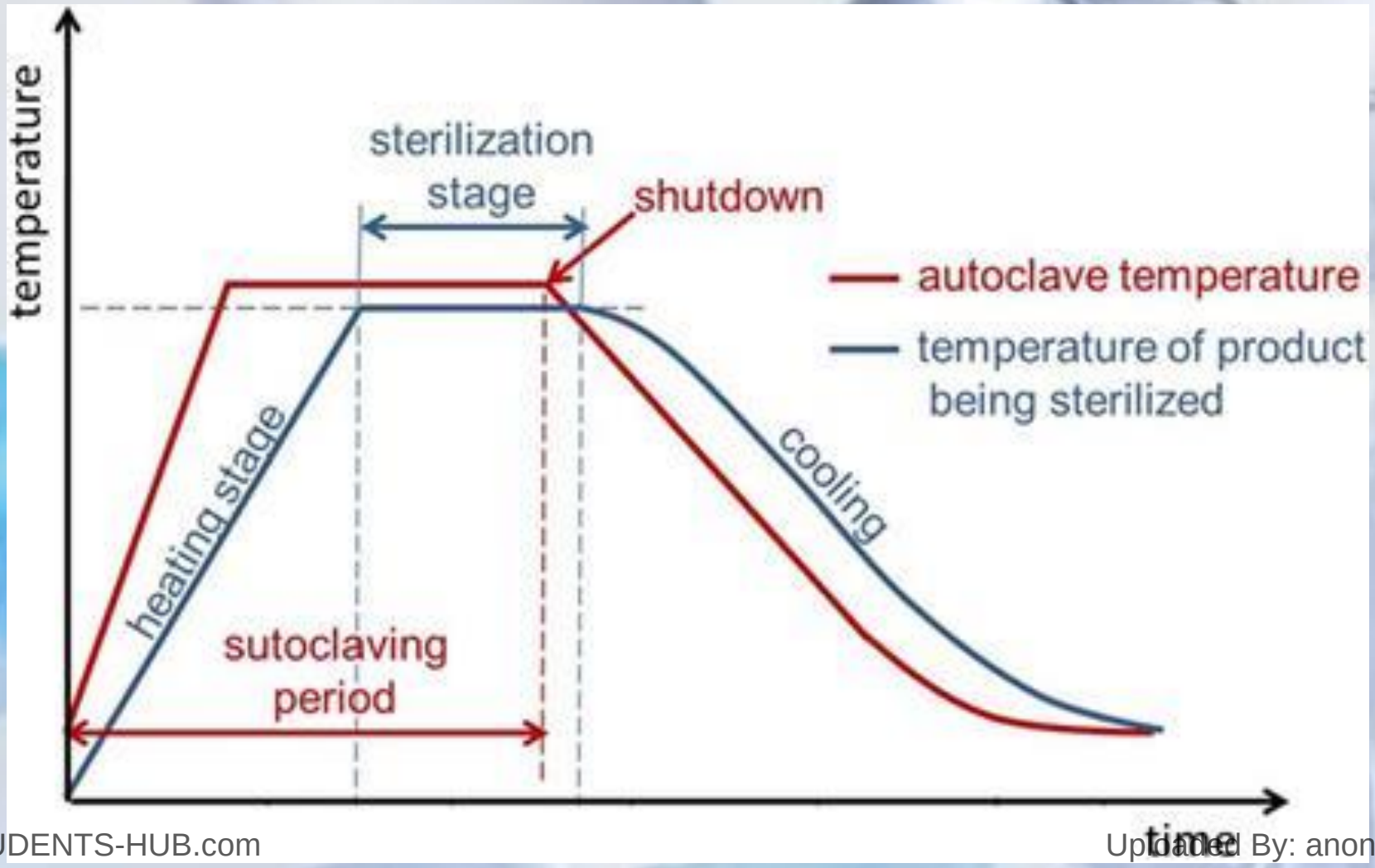
- In presence of moisture, MO are destroyed at lower temp than dry heat.

Moist heat sterilization (Steam)

The recommendations for sterilization in an autoclave are **15 minutes at 121 °C (200 kPa).**[1]

The temperature should be used to control and monitor the process; the pressure is mainly used to obtain the required steam temperature..

Temperature (°C)	Approximate corresponding pressure (kPa)	Minimum sterilization time (min)
126-129	250 (~2.5 atm)	10
134-138	300 (~3.0 atm)	5



Steam sterilization

Applications:

- -Ampoules,
- -Bulk solutions,
- -Glassware,
- -Surgical dressing, tools

Advantages

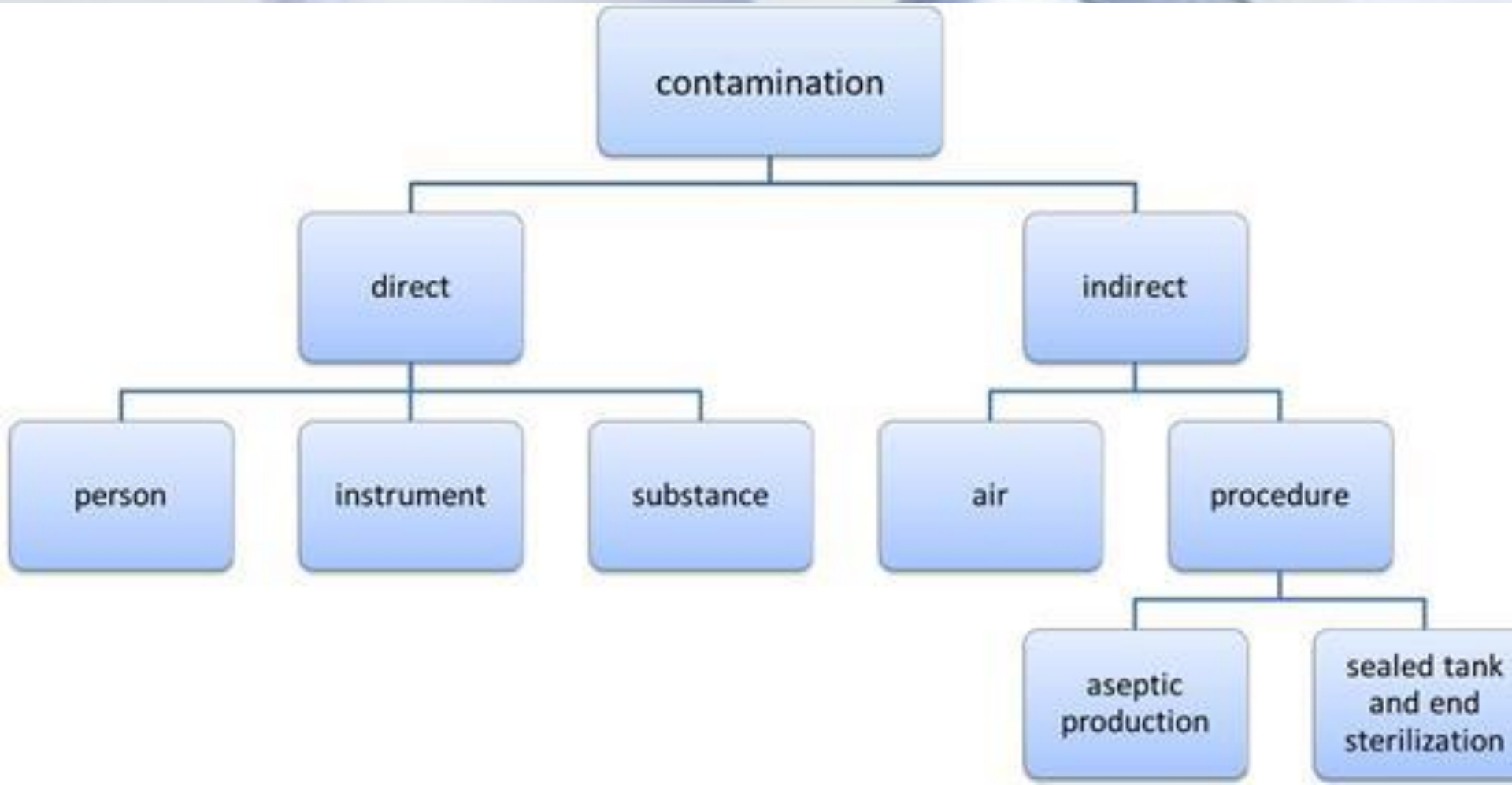
Rapid, inexpensive, effective, large volume

Disadvantages

1. cannot use for oily preparation

2. cannot use for moisture sensitive preparations

Possible sources of microbial contamination during production



Dry Heat Sterilization

heating at atmospheric pressure
fan to obtain uniform temperature by circulation.

Dry Heat Sterilization

2. Dry Heat Sterilization

Temperature (°C)	Minimum sterilization time (min)
160	180
170	60
180	30

Method: using heated air

Equipment : Oven

Mechanism of microbial destruction:

dehydration of microbial cell after oxidation

Usually conducted at 150 to 170°C for not less than 2 hours

Application: Generally employed for substances that are not effectively sterilized by moist heat such as fixed oil, glycerol, petrolatum, heat stable powder.

Sterilization by filtration

- Physical removal of **microorganisms** or by adsorption on the filter medium or sieving mechanism

Sterile filtration is the process of separating all microorganisms, from a liquid. A sterile filter must block all microorganisms in a flow of liquid without affecting product quality.

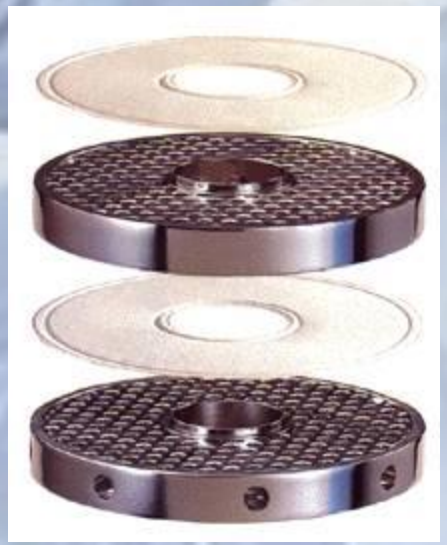
Sterilization by filtration

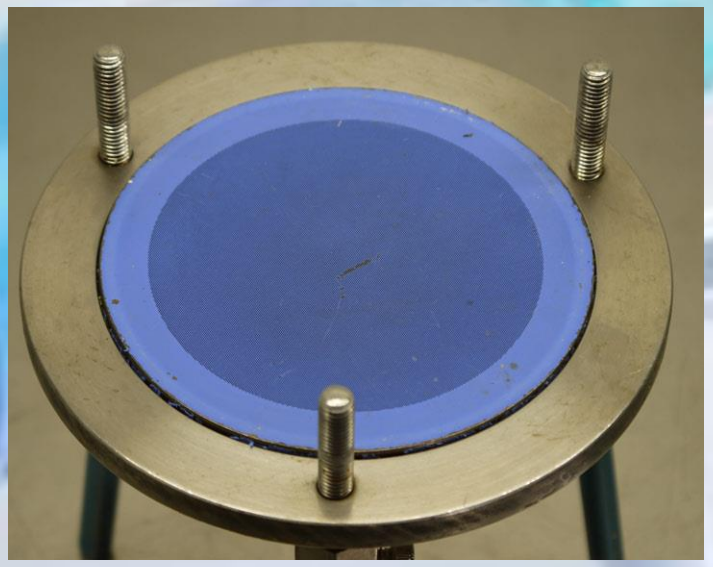
Millipore filter which is a thin plastic membrane of cellulose ester containing uniform pores constituting up to 80% of membrane's volume.

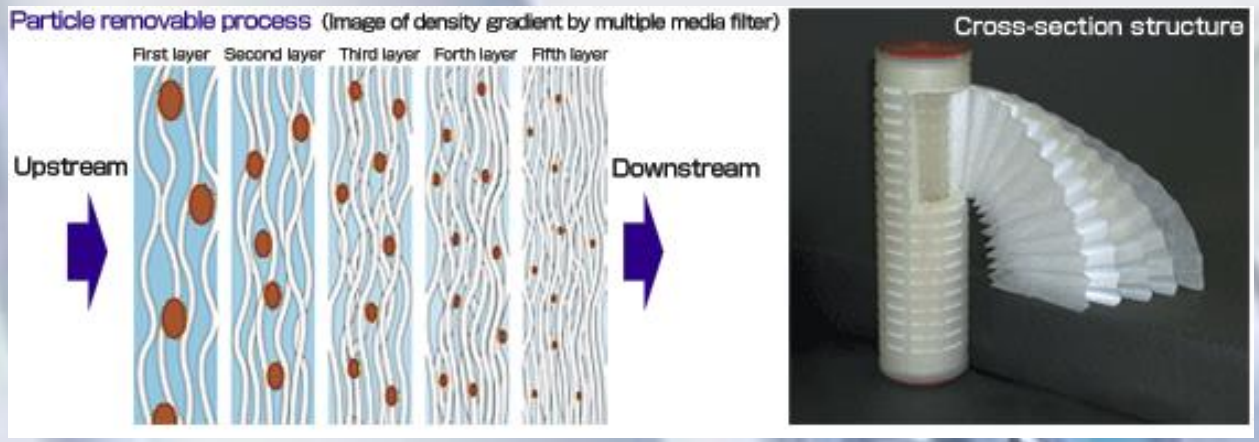
Pore size range from 14 to 0.025µm

Small bacteria is 0.22 µm, poliovirus is of 0.025 µm

filters of pore diameter 0.22 µm







Sterilization by filtration

- Depending on their size, microorganisms are not let through the pores, but instead collect on the surface. This is the most important reason, but not the only reason why filtration works.
- **Smaller particles** and microorganisms are retained in the pores due to **adsorption forces**, depending on

the pressure differential, flow rate, number of particles, surface tension, and degree of ionisation

- ***Materials used include cellulose ester, nylon, polyester, polytetrafluoroethylene, polyvinylfluoride, polycarbonate, polypropylene, polysulfone, and polyethersulfone. In addition, hydrophobic or hydrophilic membranes are used.***

Gas Sterilization

Gas sterilization involves exposure of materials/products to mixtures of ethylene oxide or propylene oxide and an inert gas, e.g. carbon dioxide within a specially designed apparatus.

Sterilization efficiency increases in the presence of moisture (up to 60%) and elevated temperature (55°C).

Mechanism of action of EO is alkylation of hydroxyl, carbonyl and amino groups of bacterial enzyme.

It reacts with amino acids, proteins and DNA, thus preventing cellular reproduction

Gas Sterilization

- Due to the highly penetrative nature of the gas medium, this technique is frequently used to sterilize medical devices (e.g. packaged catheters) and porous surgical accessories (e.g. blankets). However, this technique may also be employed for the sterilization of therapeutic agents/excipients.
- Due to the toxicity of the gas mixture, sufficient time must be allowed after sterilization to enable the sterilizing gas to be desorbed from the product/ingredient.

Sterilization by exposure to ionizing radiation

- Equipment: Ultraviolet lamp; for surface sterilization

  -Ionization (Beta rays, Gamma rays, X-rays)

- Application:
  - dry pharmaceutical products
  - heat labile product containers

Disadvantages:

1. Highly specialized equipment required
2. Effect of irradiation on product and their containers

The advantages of using radiation are the following:

1) sterilization is more effective than filtration and aseptic processing,

2) there is no residue as after for example ethylene oxide sterilization,

4) product temperature remains low,

5) easy to adjust sterilization process.

Sterilization and Disinfection

- **Sterilization** refers to the use of different procedures to **destroy all forms** of **microorganisms** including **bacterial spores**
- **Disinfection**: It is a procedure intended to reduce microorganisms as far as possible (but not bacterial spores).
- Thus, disinfection can never replace sterilization

Disinfection

Disinfection can be accomplished with:

1. Heat disinfection
2. Chemical disinfection

Heat disinfection

It is accomplished by boiling water at atmospheric pressure for at least 5 min's

Chemical disinfection

Using phenol with cleaning component destroy the membrane of microorganisms.

Using 70% alcohol or (IPA) for skin which denatures proteins of microorganisms.

Use soap containing hexachlorophene for hands.

In case of hepatitis use 5% solution of chloramines or heat disinfection

VALIDATION OF STERILITY

STERILITY TESTING FOR PARENTERAL PRODUCTS

STERILITY TEST

- Sterility testing attempts to detect the presence or absence of viable micro-organisms in a **sample number** of containers taken from batch of product.

Sterile Products - Overview

- Certain pharmaceutical products must be sterile
  - injections, ophthalmic preparations, irrigations solutions, haemodialysis solutions

- Two categories of sterile products
  - those that can be sterilized in final container (terminally sterilized)
  - those that cannot be terminally sterilized and must be aseptically prepared

Sterilization - validation

What is the definition of “sterile”?

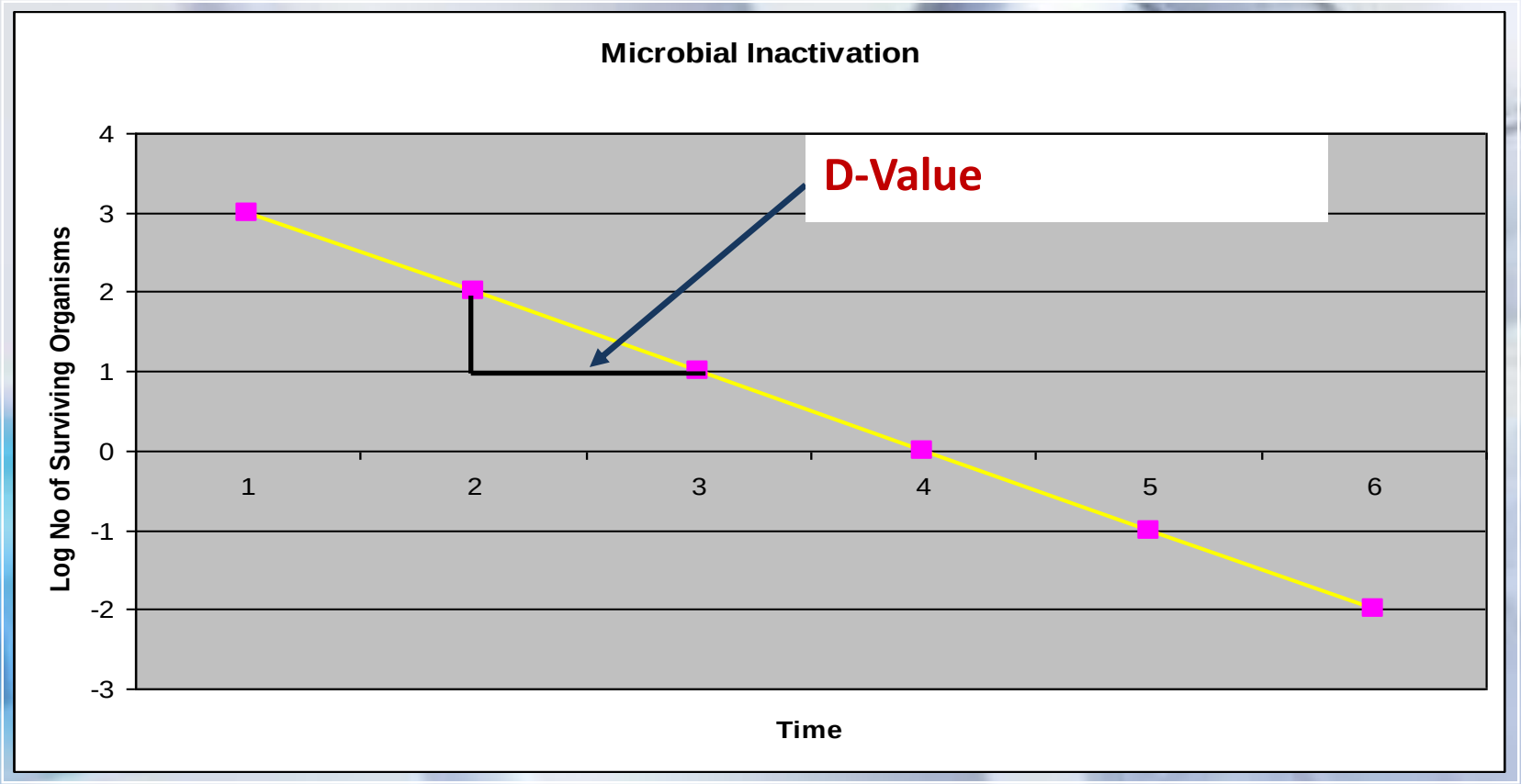
- Free from microorganisms

  In practice no such absolute statement regarding absence of microorganisms can be proven

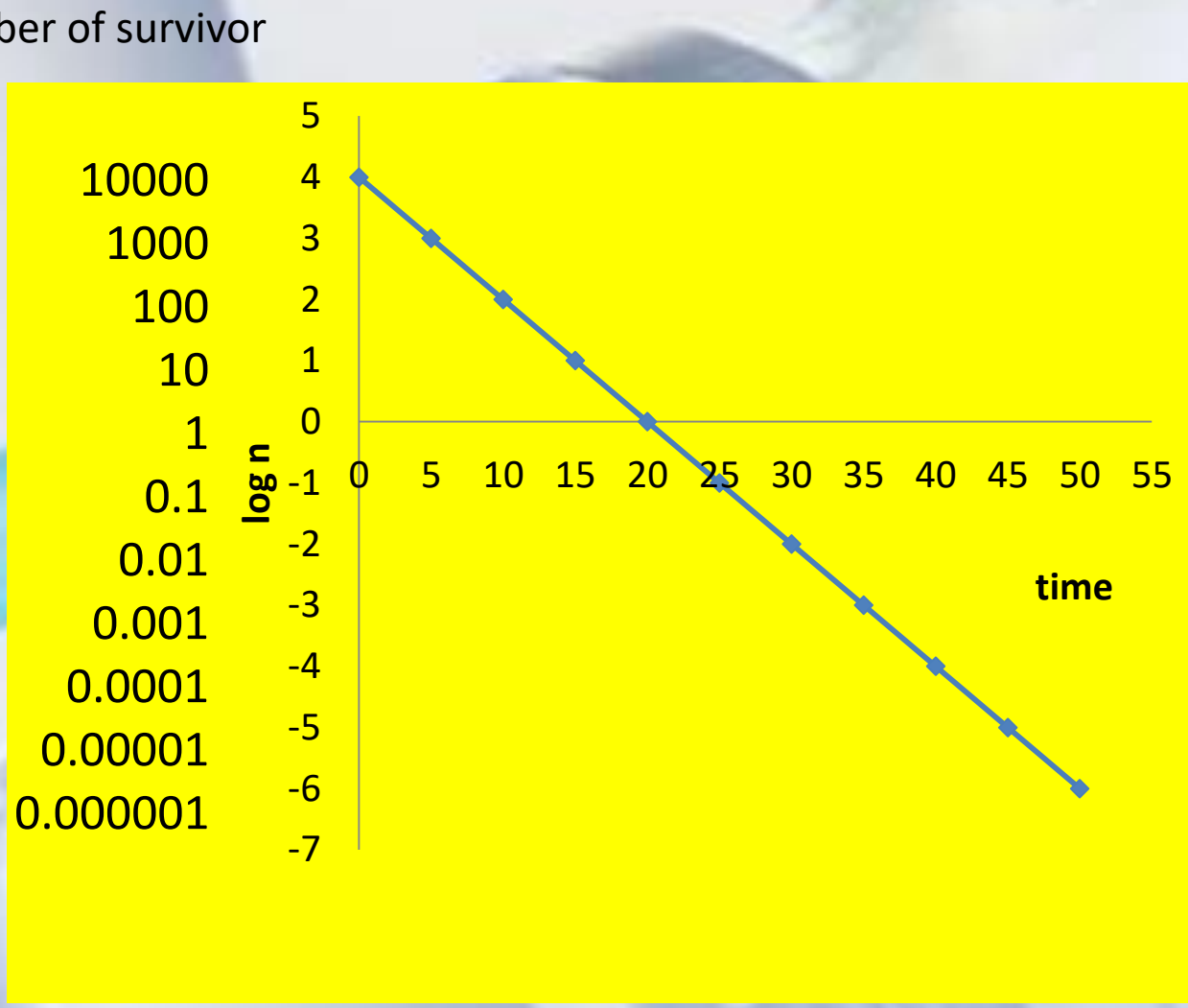
- **Defined as the probability of 1 in a million of a container being contaminated (10^{-6})**
- **This referred to as the Sterility Assurance Level (SAL)**

Sterilization - validation

D-value - Time (or dose) required to reduce the population of organisms by 1 log (or 90%)

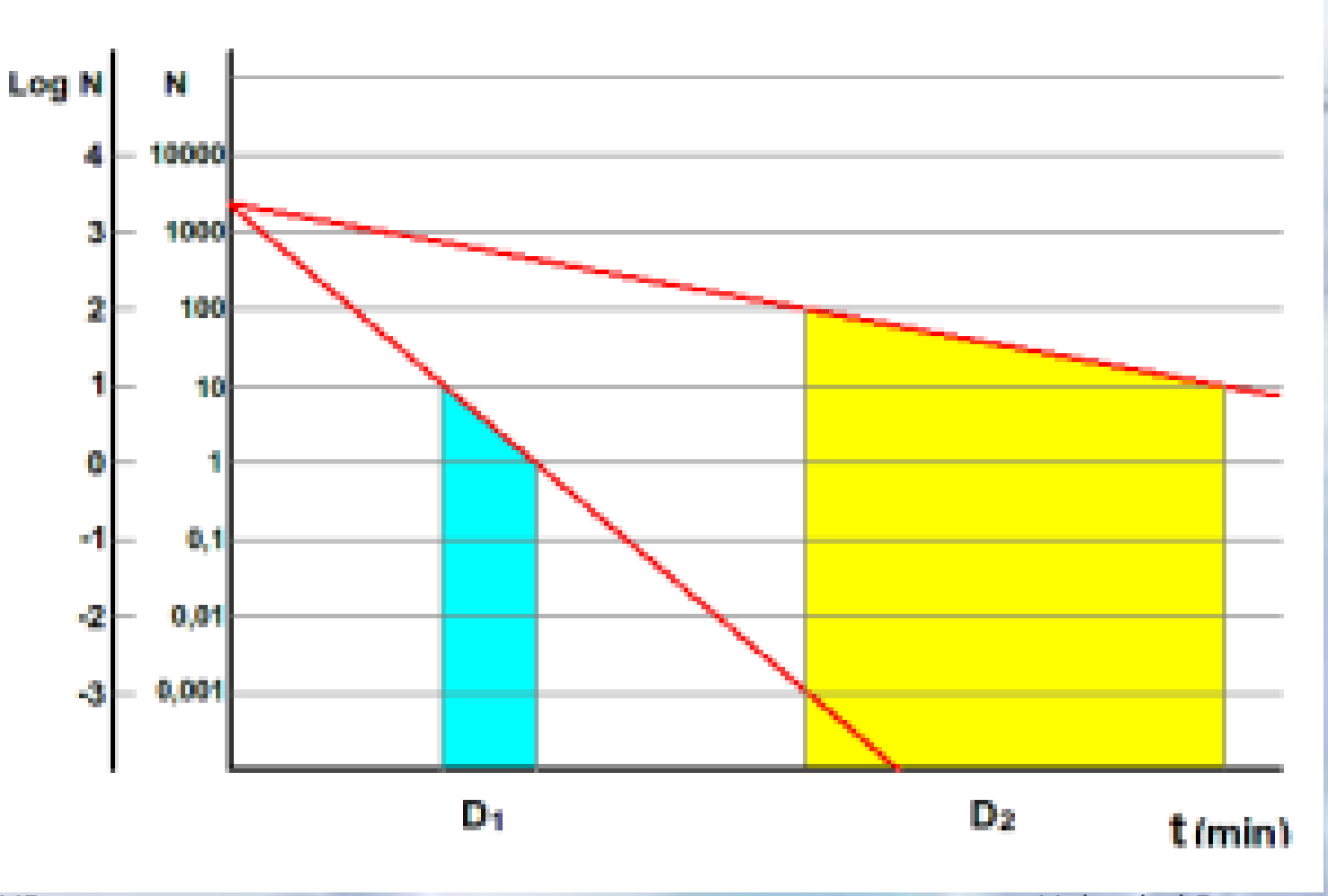


time	N Number of survivor	logn
0	10000	4
5	1000	3
10	100	2
15	10	1
20	1	0
25	0.1	-1
30	0.01	-2
35	0.001	-3
40	0.0001	-4
45	0.00001	-5
50	0.000001	-6



Sterilization - validation

D-value - Time (or dose) required to reduce the population of organisms by 1 log (or 90%)



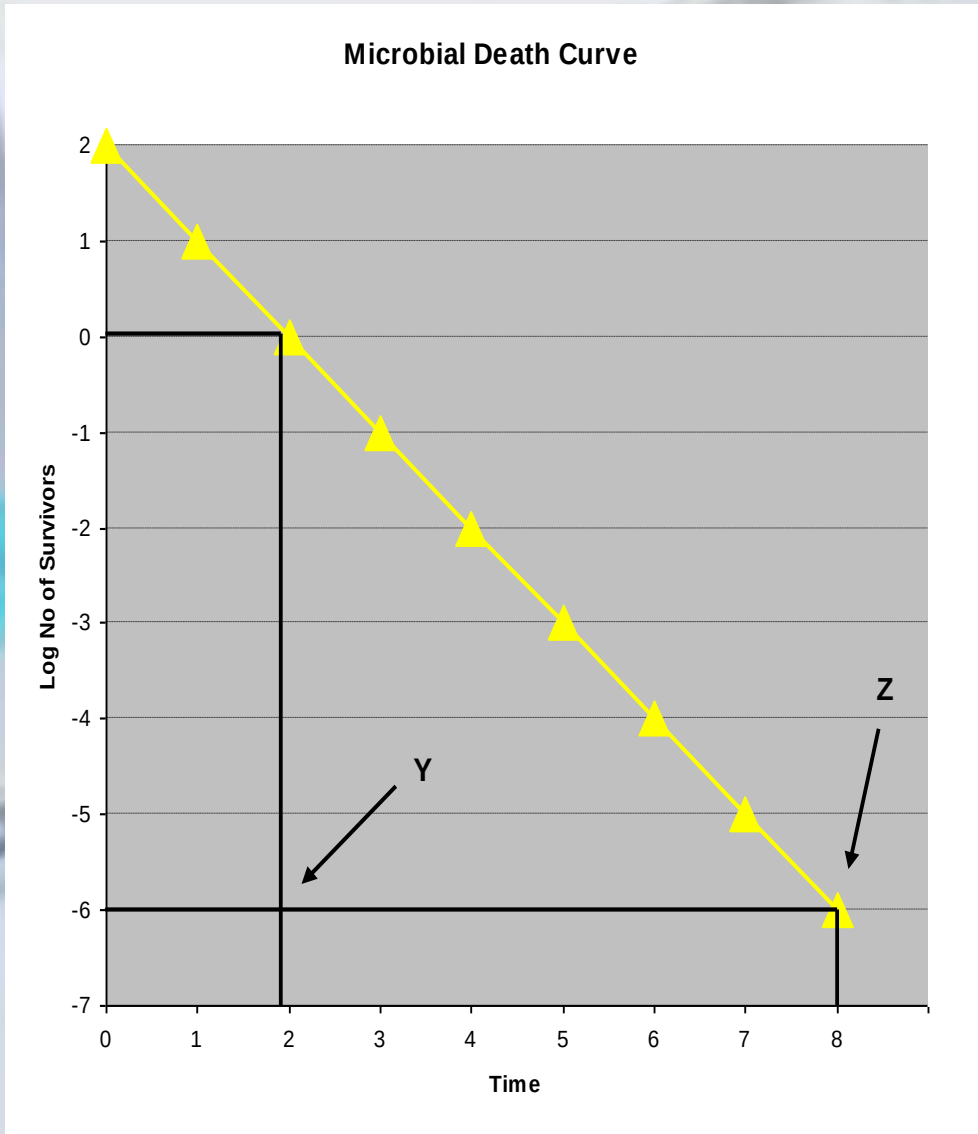
Sterilization - validation

- A sterilization process must deliver a Sterility Assurance Level (SAL) of 1 in a million **(10^{-6})**
- It is not possible to measure "10^{-6}"
- The required SAL can be achieved by applying a process that will reduce the number of organisms to zero and then apply a safety factor that will deliver an extra 6 log reduction

Sterilization - validation

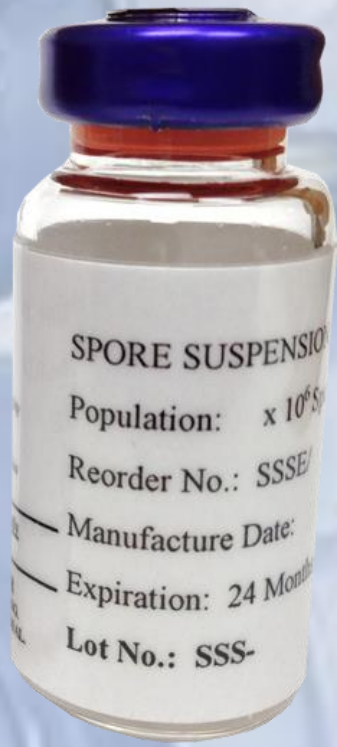
Example

- **For an initial bioburden of 10^2 the sterilization process will need to achieve an 8 log reduction in viable organisms**
- **This will require 8 times the D-value (e.g. if the organism has a D value of 2 minutes then 8 x 2 = 16 minutes will be required to achieve an 8 log reduction and an SAL of 10^{-6}) (Point Z)**



Sterilization - validation

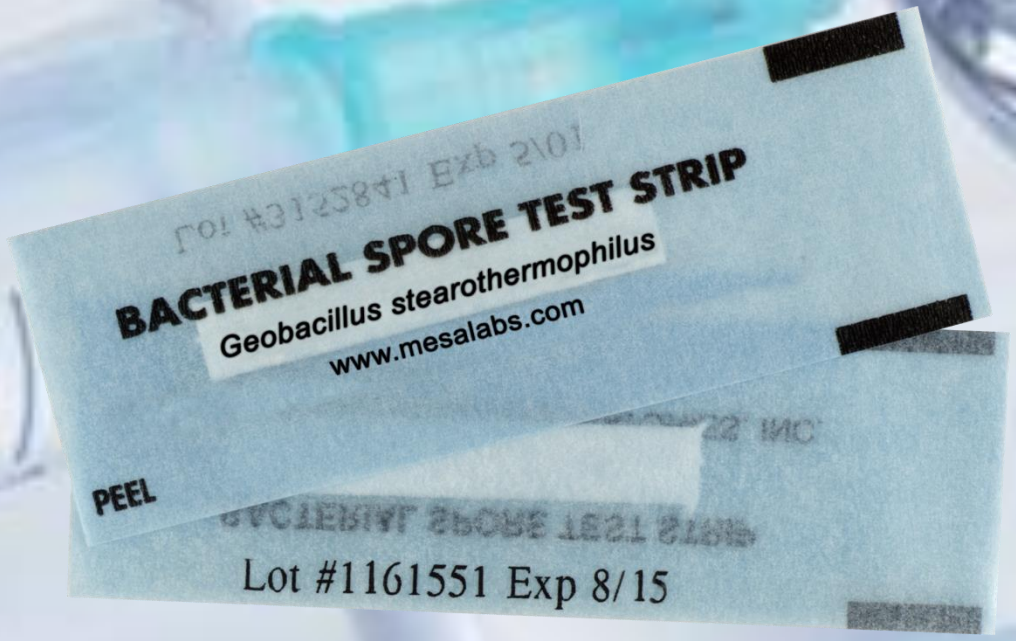
- **A biologic indicator** is a characterized preparation of specific microorganisms resistant to a particular sterilization process.



Sterilization - validation

A biologic indicator

- spores are added to a carrier, such as a strip of filter paper, packaged to maintain physical integrity while allowing the sterilization effect.



Sterilization - validation

A biologic indicator

- the spores are added to representative units of the product being sterilized, with assessment of sterilization based on these samples.

Sterilization - validation

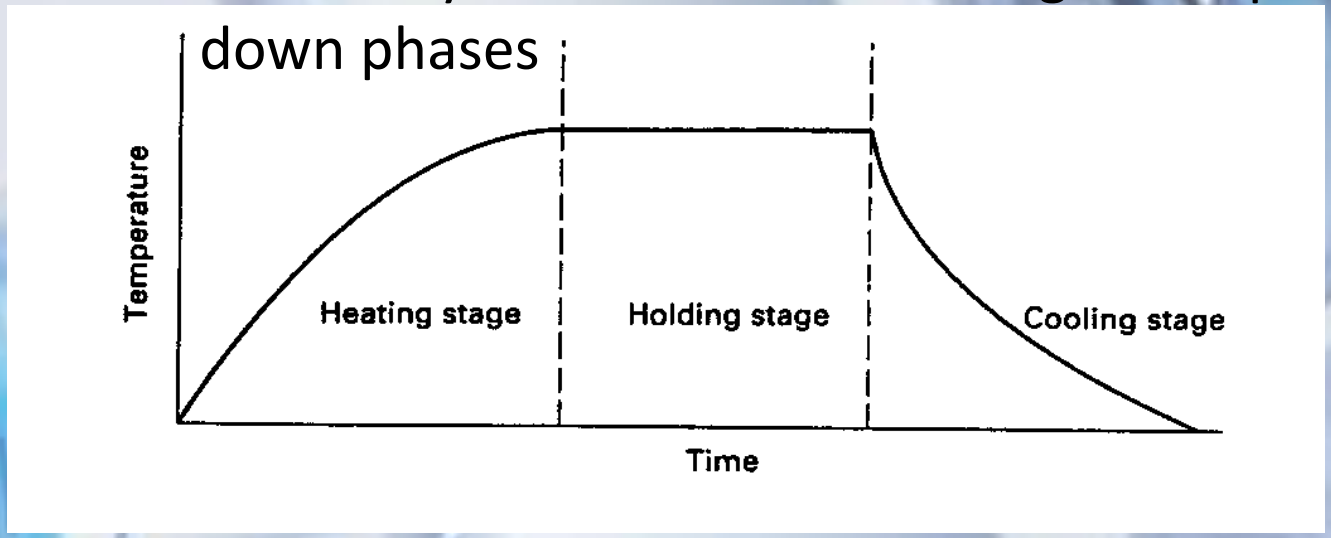
A biologic indicator

Terms relating to heat sterilisation used in fermentation industries

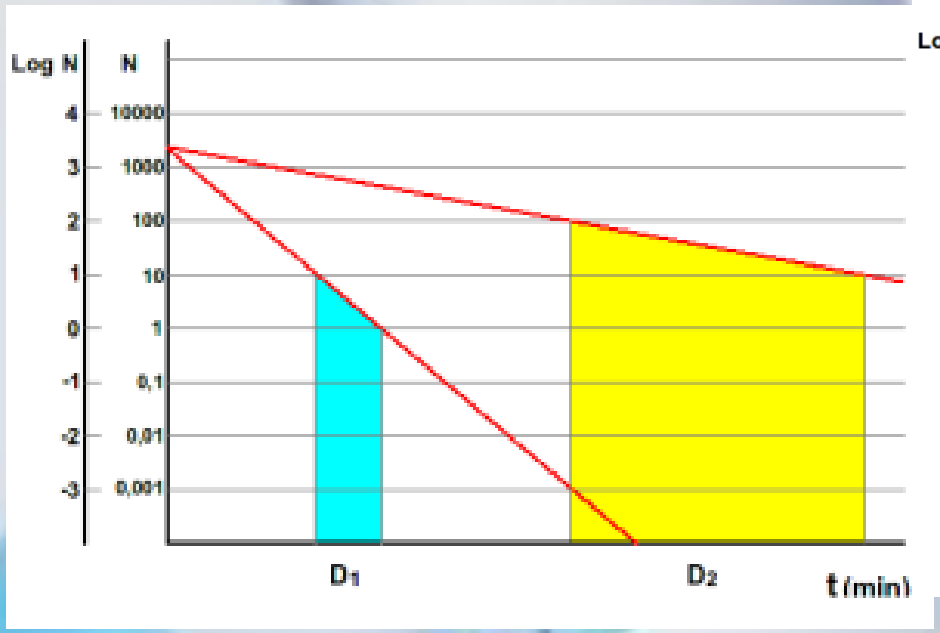
- **Thermal Death Time (TDT)** is the shortest time required to kill all microrganisms in a sample at a specific temperature and under defined conditions
- **F-value** is the time in minutes at a specific temperature (usually 250^{o}F or 121.1^{o}C) necessary to kill a population of cells or spores
- **Decimal reduction time (D-value)** is the time required to kill 90% of the microorganisms in a sample at a specific temperature

Sterilization - validation

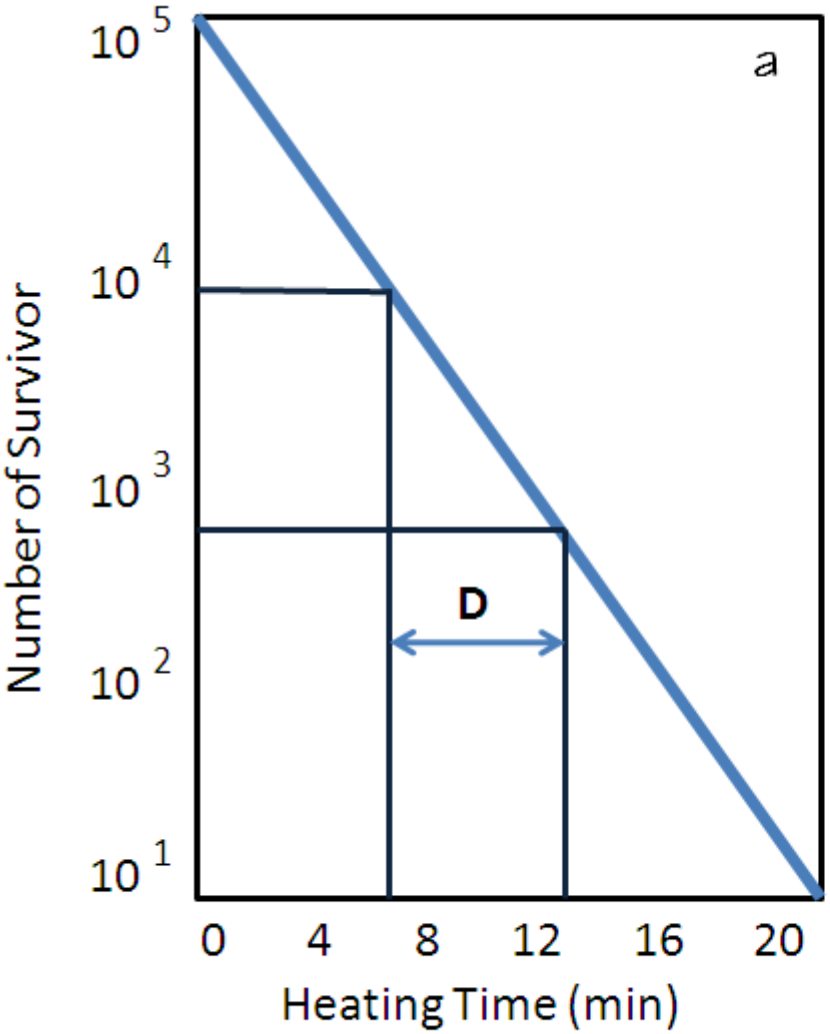
- Concept of F_o
  - Lethality factor equivalent to time at 121°C
    - 1 minute at 121°C is equivalent to F_o of 1.
    - Lethality can accumulate during heat up and cool down phases

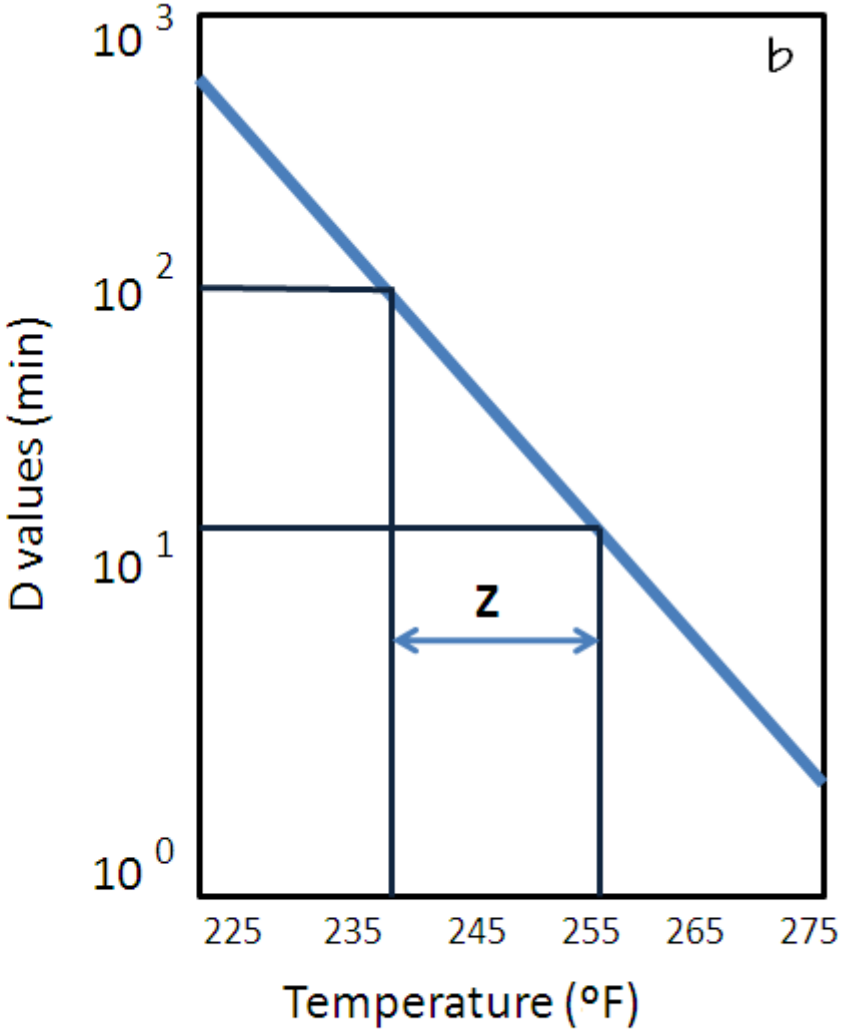


Typical temperature profile of a heat sterilization process



Z-value is the rise in temperature required to reduce D to 1/10 of its previous value





Validation - Cycle Development

- F_o Time at a particular temperature other than 121°C is the time in minutes required to provide lethality equivalent to that provided at 121°C for a stated time

$$\mathbf{F_o = D_{121} (LogA - Log B)}$$

where:

- "D_{121}" is equal to the time at 121°C to reduce the population of the most resistant organism in each product container by 90% (or 1 log)
- "A" is the number of microorganisms per container (initial microbial population)
- "B the number of microorganisms that survive after a defined heating time

VALIDATION PROCEDURE FOR THE AUTOCLAVE

$$F_0 = 10^{(T-121.1C)/10}$$

T: Temperature (C)

F_0:Equivalent Sterilization Time (minute).

$$F_0 = 10^{(T-121.1C)/10}$$

T(C)	F0(min)
121.1	1
120.8	0.933254
120.9	0.954993
121	0.977237
121.2	1.023293
121.1	1
121.3	1.047129
121.5	1.096478
120.5	0.870964
122	1.230269
	10.13362

Validation - Overview

- Selection of sterilization process must be appropriate for product
  - terminal sterilization is the method of choice
  - moist heat (autoclaving) is the most common process used for terminal sterilization
  - product must not be affected by heat
  - container/closure integrity must be established
  - items being sterilized must contain water (if sealed) or material must allow for removal of air and penetration of steam for steam (moist heat) sterilization

Validation - Protocol

Requirements for Moist Heat Sterilization

Other processes follow similar requirements

- Validation protocol should include the following details for each sterilization process
  - process objectives in terms of product type, container/closure system, SAL required
  - specifications for time, temperature, pressure and loading pattern
  - description of all equipment and support systems in terms of type, model, capacity and operating range

Validation - Protocol

- performance characteristics of all equipment e.g. pressure gauges, valves, alarm systems, timers, steam flow rates/pressures, cooling water flow rates, cycle controller functions, door closure gasketing and air break systems and filters
- methodology for monitoring performance of equipment and the process and laboratory testing methodology
- personnel responsible for all stages and final evaluation (should have experience and necessary training and be authorized)

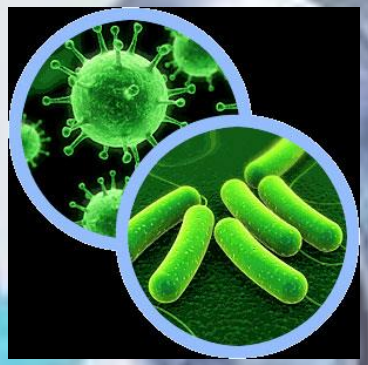
Factors of importance in sterility testing

- The **environment** in which the test is conducted
- The **quality of the culture** conditions provided
- The **test method**
- The **sample size**
- The **sampling procedure**

Sterility testing

Factors affecting growth of bacteria

- Nutrition
- Moisture
- Air
- Temperature
- pH
- Light
- Osmotic pressure
- Growth inhibitors



Sterility testing

- Pyrogen test
- Clarity test
- leak test(immerse the ampl. in a dye (methylene blue) apply vacuum in-side the ampl. if dye go inside there is leakage)

PYROGENS AND PYROGEN TESTING

PYROGENS AND PYROGEN TESTING

- Produced mostly by gram-negative bacteria
- Endotoxin - complex of pyrogenic **lipopolysaccharide**, a protein and inert lipid;
- lipid part of the lipopolysaccharide is the main pyrogenic agent; polysaccharide Water soluble

The endotoxin characteristics

- thermostable
- water-soluble
- unaffected by the common bactericides
- non-volatile
- These are the reasons why pyrogens are difficult to destroy once produced in a product

PYROGENS AND PYROGEN TESTING

Sources of pyrogen contamination

- solvent
- Raw materials
- Environment
- Containers and closures
- Personal
- Storage between preparation and sterilization

PYROGENS AND PYROGEN TESTING

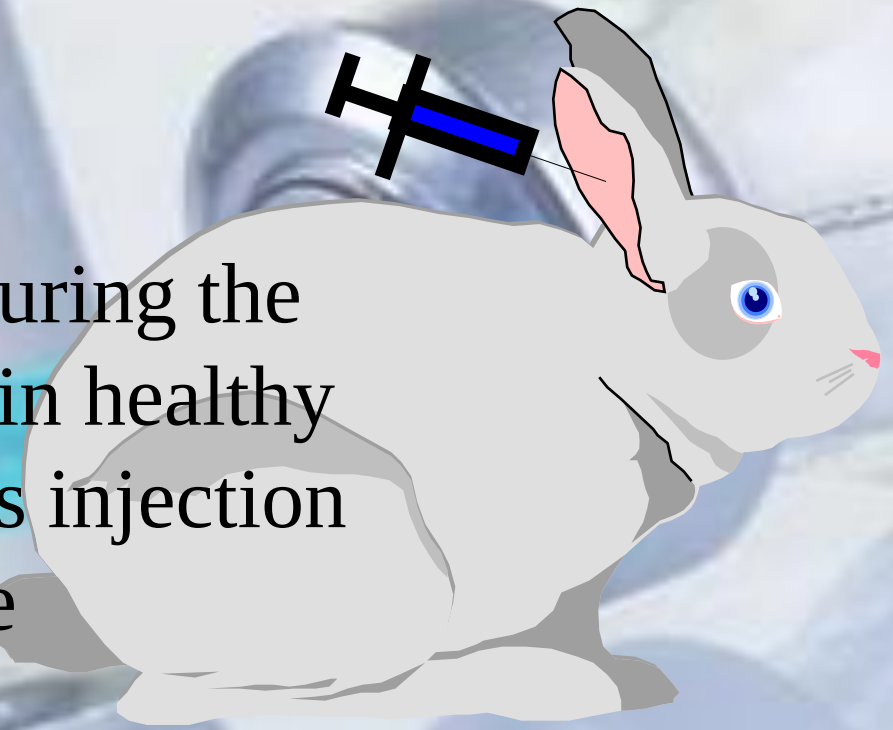
- Test for pyrogens = Rabbit test

- limulus amebocyte lysate (LAL)

  The Bacterial Endotoxins Test (BET)

Horseshoe Crab

Test for pyrogens = Rabbit test



The test consists of measuring the rise in body temperature in healthy rabbits by the intravenous injection of a sterile solution of the substance under the test.

Why the Rabbit?

- Reproducible pyrogenic response
- Similar pyrogenic response to humans
- Other species not predictable

Test for pyrogens = Rabbit test

- Preliminary test (Sham Test)
  - intravenous injection of sterile pyrogen-free saline solution
  - to exclude any animal showing an unusual response to the trauma (shock) of injection
  - any animal showing a temperature variation greater than 0.6°C is not used in the main test

Test for pyrogens = Rabbit test

- main test:
  - group of 3 rabbits
  - preparation and injection of the product:
    - warming the product 37 C
    - dissolving or dilution
    - duration of injection: not more than 10 min
    - the injected volume: **10 ml per kg** of body mass
  - determination of the initial and maximum temperature
    - all rabbits should have initial T: from 38.0 to 39.8°C
    - the differences in initial T should not differ from one another by more than **1°C**

The result of pyrogen test:

If no rabbit shows an individual rise in temperature of 0.5°C or more, the product meets the requirements for the absence of pyrogens.

If any rabbit shows an individual temperature rise of 0.5°C or more, continue the test using **five other rabbits**.

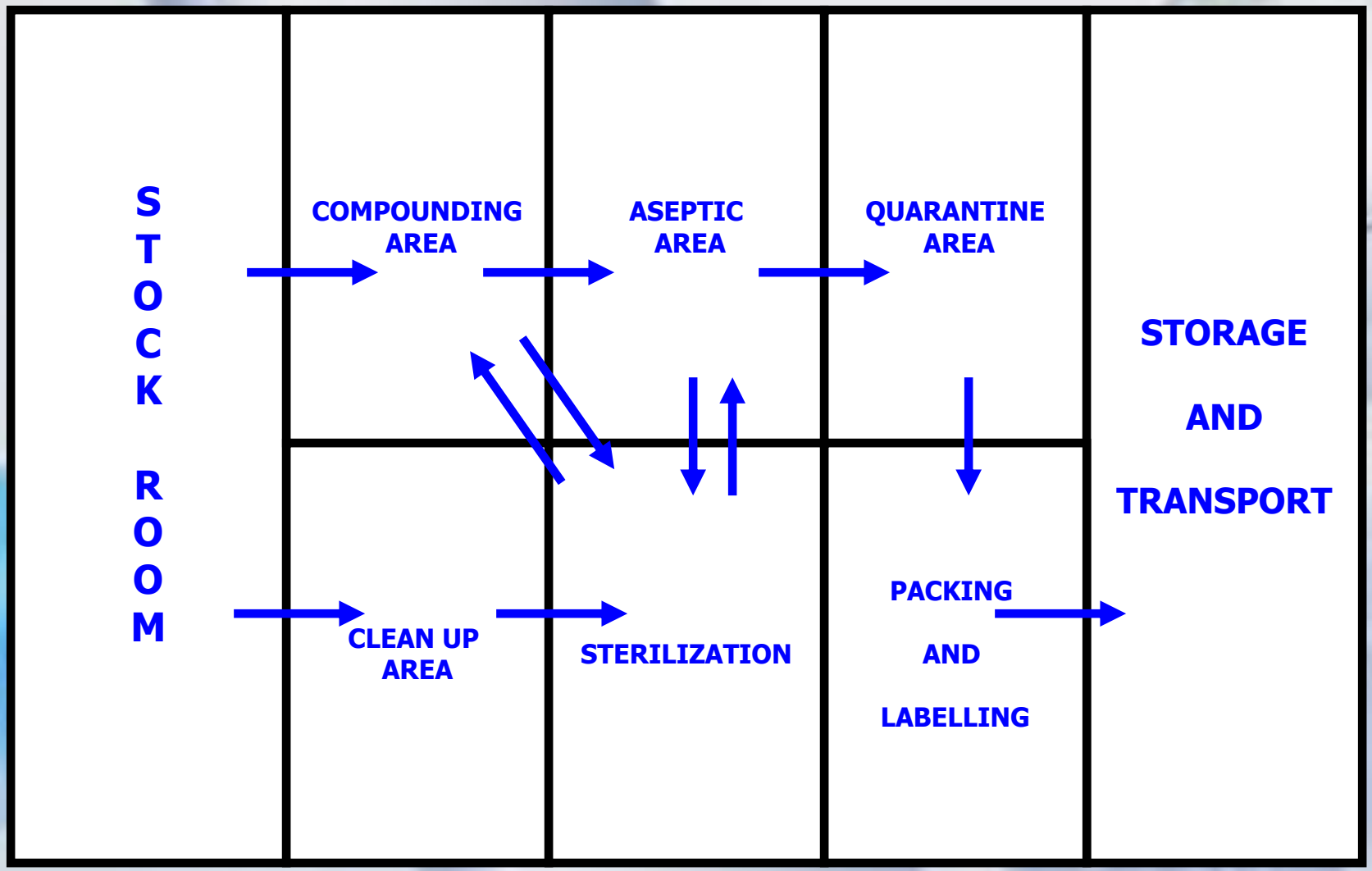
If **not more than three** of the eight rabbits show individual rises in temperature of 0.5°C or more and if **the sum of the eight individual** maximum temperature rises does not exceed 3.3°C, the material under examination meets the requirements for the absence of pyrogens

If above test not passes, the sample is said to be pyrogenic

limulus amebocyte lysate (LAL) Bacterial Endotoxins Test (BET)

- An extract from the blood cells of the horseshoe crab (*Limulus polyphemus) contains an enzyme* and protein system that coagulates in the presence of low levels of lipopolysaccharides.

LAY OUT OF PARENTERAL MANUFACTURING AREA



Industrial preparation

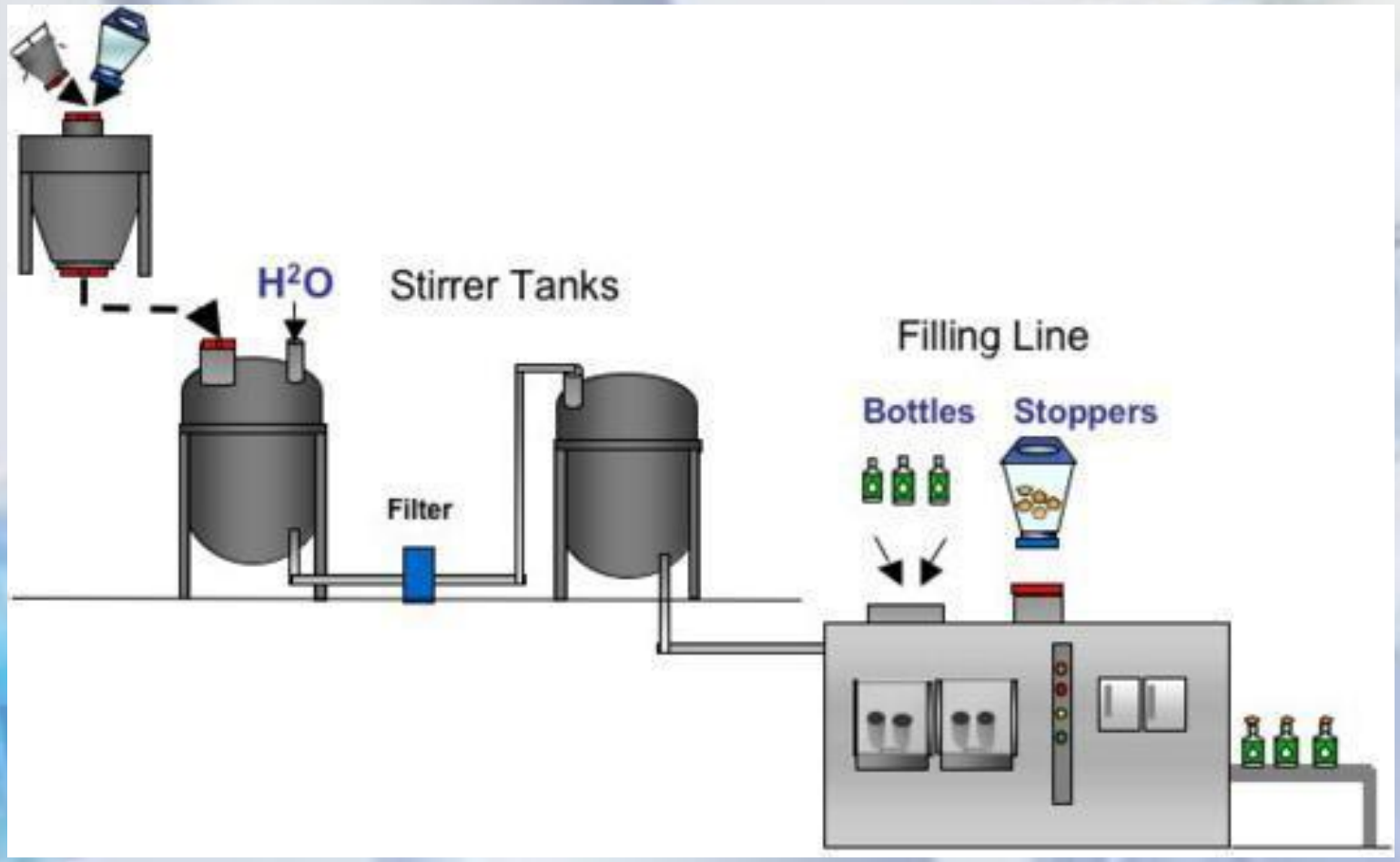
1. Cleaning
2. Preparation of bulk products
3. Filtration
4. Filling of solution in or product in ampoule or vial
5. Sealing
6. Sterilization
7. Tests for Quality control

Industrial preparation

1-Thermostable ➡ Filtration ➡ subdivided into the final container ➡ sealed ➡ terminal sterilization by autoclave

2-Thermolabile ➡ filtration for sterilization ➡ subdivided into the final container ➡ sealed

Industrial preparation



Production of parenteral solutions

Issues considered for routine production

- Manufacturing environment should be controlled
- Procedures in place to minimize the pre-sterilization pyrogen
- Time between filling and sterilization should be specified
- Integrity of container/closure system should be periodically verified
- Periodic leak testing of chamber (if vacuum is part of cycle)

Production of parenteral solutions

- Differentiation between sterilized and not-yet sterilized product
  - Physical separation (double ended autoclave)
  - Labelling and use of visual indicators (e.g autoclave tape)
- Periodic testing of containers to verify integrity of container/closure system
- Quality of steam should be defined and periodically tested for contaminants

Production of parenteral solutions

- Each sterilization cycle must be monitored
  - temperature, time and pressure recorded
  - temperature recorder independent from cycle controller
  - second independent temperature recorder
  - drain temperature should be recorded
  - chemical and biololgical indicators (if applicable)
- Sterilisation cycle records should form part of batch records

Methods of monitoring particulate matter contamination

- consisting of two methods: Light Obscuration and Microscopic.

Visual method

Filtration method

Particle Counting in Parenteral Solutions

	Small Volume Parenterals	Large Volume Parenterals	Dry Powders
British Pharmacopoeia	None	<100/ml @ 5µm, <50/ml @10µm	None
US Pharmacopoeia	<6000 @ 10µm <600 @ 25µm per container	<25/ml @ 10µm <3/ml @ 25µm	None
European Pharmacopoeia	<6000 @ 10µm <600 @ 25µm per container	<25/ml @ 10µm <3/ml @ 25µm	<10,000 @ 10µm, <1000 @ 25µm per container

Table 1. ISO Classification of Particulate Matter in Room Air (limits are in particles of 0.5 µm and larger per cubic meter [current ISO] and cubic feet [former Federal Standard No. 209E, FS 209E])*

Class Name		Particle Count	
ISO Class	U.S. FS 209E	ISO, m^3	FS 209E, ft^3
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1,000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

PACKAGING OF PARENTERAL

A. Single dose container

B. Multiple dose container

Packaging

1. Glass ampoules

2. Rubber Stoppard vials

3. Glass and plastic bottles

4. Glass and plastic syringes

5. Prefilled syringes

PACKAGING OF PARENTERAL

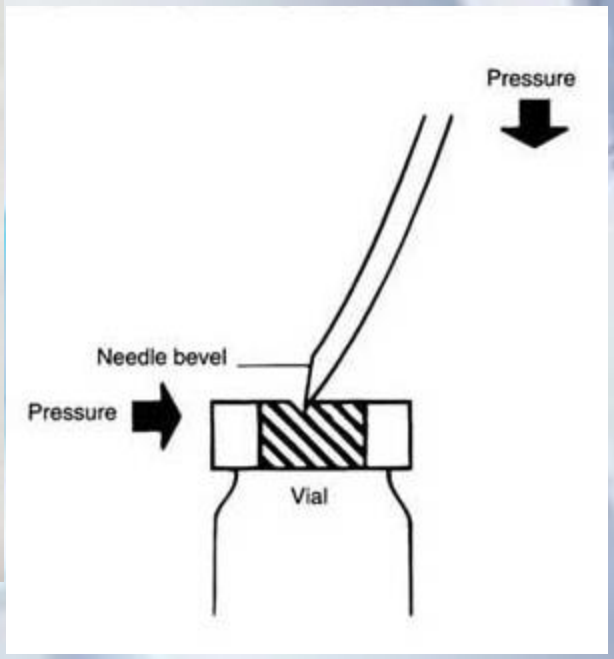
single dose container

PACKAGING OF PARENTERAL

- Hermetic (sealed by heat fusion)
- It could be ampoules or vials
- The type of glass or plastic used is indicated in the individual monograph of that preparation.

PACKAGING OF PARENTERAL

Multiple dose container



Types of packaging

1-Glass

2-Plastic

3. Rubber

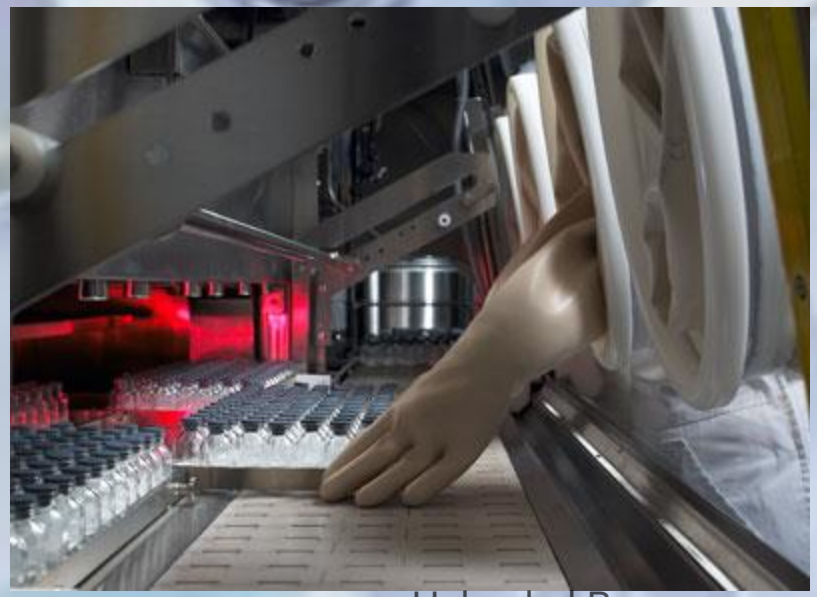
Good elasticity

Ability to reseal after puncture

Adaptability to various shape

Clarity test

- Test the presence of visible particles › 50 µm in the injection
- The injections are tested visually by human inspection under good light against white and black backgrounds



LABELING

–Name of product
–Quantity of the product
–% of drug or amount of drug in specified volume of amount of drug and volume of liquid to be added
–Name and quantity of all added substances??????????
–Mfg. license no.
-Route of administration
- Storage conditions
–Batch no.
–Manufacturer/Distributor
–Mfg. & Expiration date
–Retail price (incl. of all taxes)
–Veterinary product should be so labeled

QUALITY ASSURANCE FOR PHARMACY PREPARED STERILE PRODUCTS USP <797>

provide the minimum practice and quality standards for compounded sterile preparations (CSPs)

Appropriate risk level (low, medium, high) assigned according to corresponding probability of contamination with:

- Microbial (organisms, spores, endotoxins)
- Chemical or Physical (foreign chemicals or physical matter)

Goal of Chapter <797>

- Goal of USP Chapter <797> is to prevent potential patient **harm** or **death** that could result from:
  - Microbial contamination
  - Excessive bacterial endotoxins
  - Large content errors in the strength of correct ingredients
  - Incorrect ingredients

Definition of Compounded Sterile Products (CSP) – USP27 <797>

- Preparations prepared according to the manufacturer's labeled instructions and other manipulations that expose contents to potential contamination
- Preparations containing nonsterile ingredients or employ nonsterile components or devices that must be sterilized before administration
- Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess either of the above two characteristics

Scope of USP <797> Multidisciplinary

Chapter USP <797> applies to pharmacists, physicians, nurses, and allied health team members.

Selected Sections of Chapter <797>

- Personnel cleansing and gowning
- Responsibilities of compounding personnel
- Risk level classification of Compounded Sterile Products (CSP) and quality assurance
- Verification of accuracy and sterilization of CSP
- Personnel training and assessment
- Environmental quality and control
- Equipment
- Storage and beyond-use dating

Personnel Cleansing and Gowning

- Hand Washing
  - Wash hands, nails and arms up to the elbow with soap and water
  - Wash for at least 15 seconds (Sing alphabet song)
  - Use a disposable scrub brush to clean nails and between fingers
  - Dry hands with non-shedding towel
  - Turn off faucet with towel or use foot pedals

Personnel Cleansing and Gowning (cont.)

- After washing hands, put on non-shedding uniform components in this order:
  - Knee-length coats or coveralls
  - Hair cover
  - Shoe covers
  - Protective gloves
  - Face mask when in hood

Personnel Cleansing and Gowning (cont.)

- Hair Covers
  - Must cover all hair
  - Beards and long sideburns require use of beard cover
- Gloves
  - Powder free
  - Clean new gloves with 70% isopropyl alcohol before use
  - Avoid touching non-sterile surfaces
  - Intermittently sanitize gloves with 70% isopropyl alcohol

Personnel Cleansing and Gowning (cont.)

- Every time you leave the buffer area you must **remove** and **discard** your:
  - Hair cover
  - Gloves
  - Face mask

- Must remove lab coat when leaving buffer area
  - May hang coat inside out
  - Must discard coat at the end of each shift

Personnel Cleansing and Gowning (cont.)

- Face mask must be worn while in hood
  - Minimizes airborne contaminants while talking, sneezing and coughing
  - Must cover mouth and nose completely

Responsibilities of Compounding Personnel

- Manipulate sterile products aseptically
- Ensure products are accurately
  - Identified
  - Measured
  - Diluted
  - Mixed
- Maintain appropriate cleanliness conditions
- Ensure products are correctly
  - Purified
  - Sterilized
  - Packaged
  - Sealed
  - Labeled
  - Stored
  - Dispensed
  - Distributed

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QUALITY ASSURANCE FOR PHARMACY PREPARED STERILE PRODUCTS USP <797>

provide the minimum practice and quality standards for compounded sterile preparations (CSPs)

- Appropriate risk level (low, medium, high) assigned according to corresponding probability of contamination with:
  - Microbial (organisms, spores, endotoxins)
  - Chemical or Physical (foreign chemicals or physical matter)
  - Risk level determined by professional judgment

Risk Level Classifications of Compounded Sterile Products

Low-Risk Level

- Products compounded with aseptic manipulations entirely within **ISO class 5** quality air using only sterile ingredients, products, components or devices
- Involves transfer, measuring, and mixing manipulations with closed or sealed packaging systems
- Manipulations limited to aseptically opening ampoules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to other sterile products

Risk Level Classifications of Compounded Sterile Products

- Examples of Low-Risk Compounding
  - Single transfers of sterile dosage forms from ampoules, bottles, bags, and vials using sterile syringes with sterile needles, and other sterile containers. The contents of ampoules requires sterile filtration to remove glass particles
  - Manually measuring and mixing no more than three manufactured products to compound drug admixtures
  - Tobramycin piggyback
  - Morphine drip

Risk Level Classifications of Compounded Sterile Products (cont.)

Low-Risk Level Characteristics (cont.)

- Quality Assurance
  - Routine disinfection of the direct compounding environment to minimize microbial surface contamination
  - Visual conformation that personnel are properly garbed with hair covers, gloves, masks, etc.
  - Review of all products to ensure correct identity and amounts of ingredients were compounded
  - Visual inspection of products to ensure the absence of particulates in solutions, the absence leakage from vials or bags, accuracy of labeling

Risk Level Classifications of Compounded Sterile Products

medium-risk level

Medium-Risk Conditions include all low-risk conditions in addition to one or more of the following:

- Multiple individual or small doses of sterile products are combined to prepare a product that will be administered to multiple patients or the same patient on multiple occasions
- Compounding includes complex aseptic manipulations other than single volume transfer
- Compounding requires unusually long duration to complete dilution or homogenous mixing
- The product does not contain bacteriostatic substances and is administered over several days (e.g. external or implanted pump)

Risk Level Classifications of Compounded Sterile Products

medium-risk level

- Examples Medium-Risk Compounding
  - Compounding of total parenteral nutrition using manual or automated devices
  - Filling of reservoirs of injection and infusion devices
    - with multiple sterile products
    - administered over several days at ambient temperatures (implanted pumps)
  - Transfer of volumes from multiple ampoules or vials into a single, final sterile container or product

Risk Level Classifications of Compounded Sterile Products (cont.)

Medium-Risk Level Characteristics (cont.)

- Quality Assurance
  - Routine disinfection of the direct compounding environment to minimize microbial surface contamination
  - Visual conformation that personnel are properly garbed with hair covers, gloves, masks, etc.
  - Review of all products to ensure correct identity and amounts of ingredients were compounded
  - Visual inspection of products to ensure the absence of particulates in solutions, the absence leakage from vials or bags, accuracy of labeling

Risk Level Classifications of Compounded Sterile Products

High risk level

High-Risk Conditions include **all** low-risk and medium-risk conditions in addition to one or more of the following

- Non-sterile ingredients are incorporated or a non-sterile device is employed before terminal sterilization
- Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO class 5
- Non-sterile preparations are stored greater than 6 hours before being sterilized

Risk Level Classifications of Compounded Sterile Products (cont.)

High-Risk Level Characteristics (cont.)

- Examples of High-Risk Compounding
  - Dissolving non-sterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized
  - Exposure of sterile ingredients to air less than ISO class 5 (e.g. nursing preparation on the ward)
  - Measuring or mixing of sterile ingredients in non-sterile devices before sterilization is performed

Risk Level Classifications of Compounded Sterile Products (cont.)

High-Risk Level Characteristics (cont.)

- Quality Assurance
  - Routine disinfection of the direct compounding environment to minimize microbial surface contamination
  - Visual conformation that personnel are properly garbed with hair covers, gloves, masks, etc.
  - Review of all products to ensure correct identity and amounts of ingredients were compounded
  - Visual inspection of products to ensure the absence of particulates in solutions, the absence leakage from vials or bags, accuracy of labeling

Risk Level Classifications of Compounded Sterile Products

Quality Assurance

- Routine disinfection of the direct compounding environment
- Visual conformation that personnel are properly garbed with hair covers, gloves, masks, etc.
- Review of all products to ensure correct identity and amounts of ingredients were compounded
- Visual inspection of products to ensure the absence of particulates in solutions, the absence leakage from vials or bags, accuracy of labeling

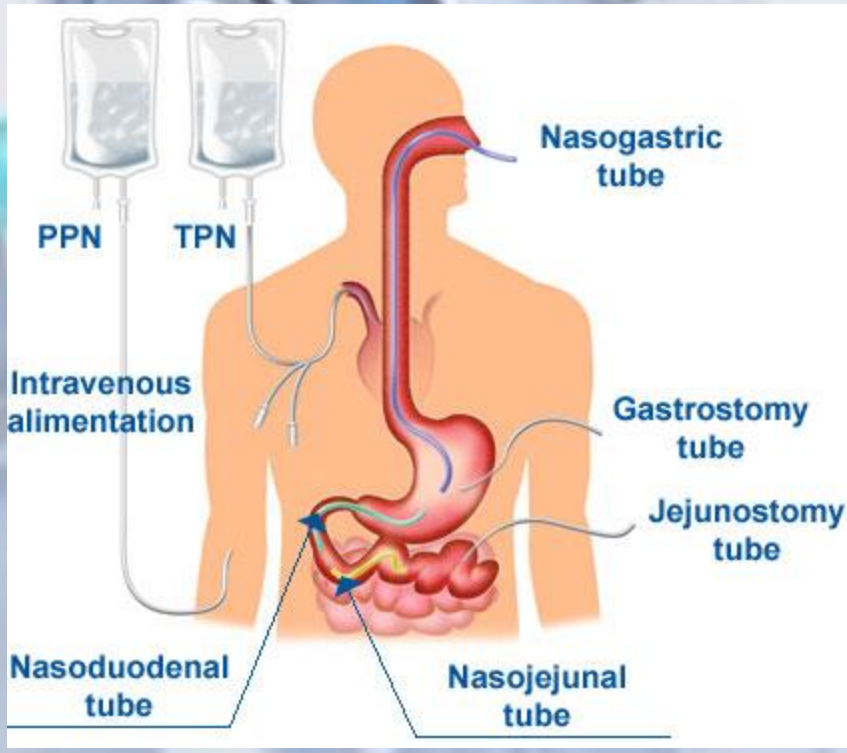
Total Parenteral Nutrition

- TPN stands for Total Parenteral Nutrition. This is a complete form of nutrition, containing protein, sugar, fat and added vitamins and minerals as needed for each individual.
- **PPN (peripheral parenteral nutrition)**

Both the TPN and the PPN are provided by IV

Total Parenteral Nutrition means total nutrition, which is provided when a patient does not receive any other form of nutrition. When a patient is on Total Parenteral Nutrition, he relies on it completely.

Peripheral Parenteral Nutrition, or PPN, is only partial. This means that the patient may be getting nutrition from other sources along with the PPN.



Difference Between TPN and PPN

1. Total Parenteral Nutrition is total nutrition, which is provided when a patient does not receive any other form of nutrition. Peripheral Parenteral Nutrition is only partial, which means that the patient may be getting nutrition from other sources.
2. TPN comes in a higher concentration, and can be administered through larger veins. PPN comes in a lesser concentration, and can be delivered using a peripheral vein.
3. When compared to TPN, the PPN is not a preferred nutritional supplement for a long time.
4. TPN comes in a higher concentration of components when compared to PPN.