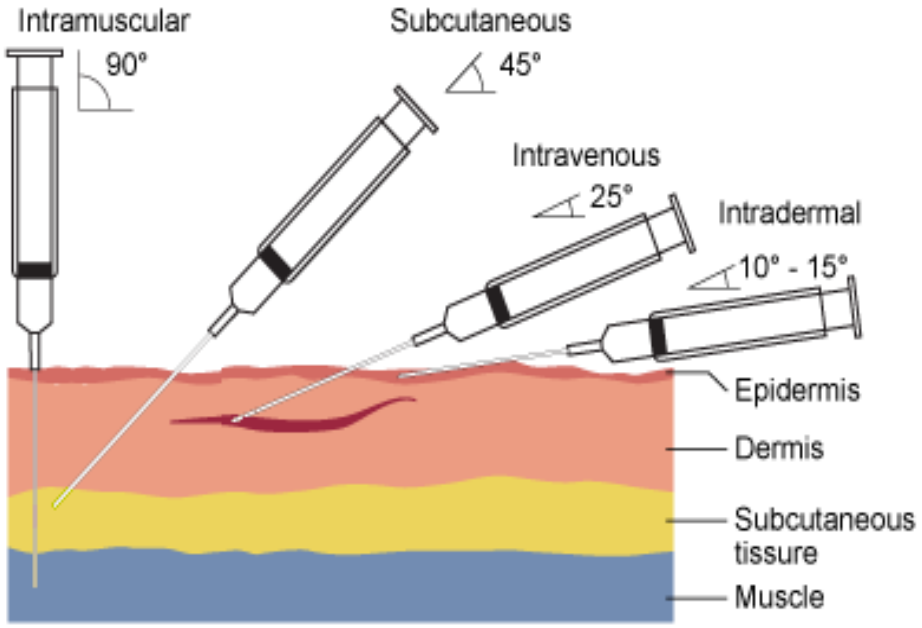
Sterile Products

Sterile Products

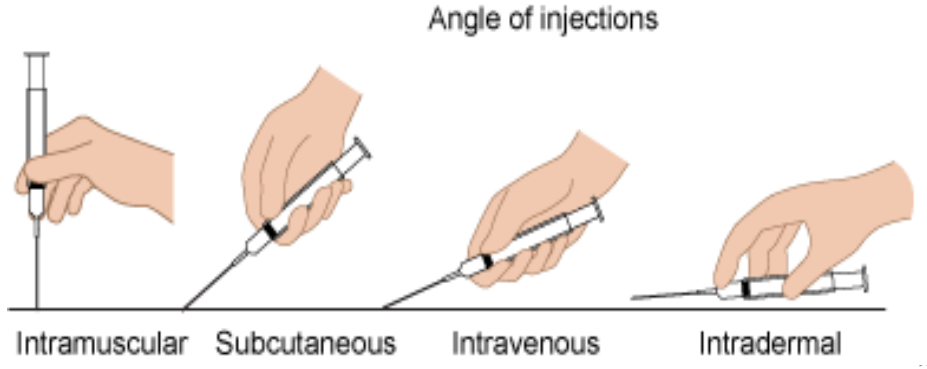
- These are dosage forms of therapeutic agents that are **free** of viable microorganisms (MO).
- These include: **Parenteral**, **ophthalmic**, and **irrigating** preparations.
- Parenteral products are unique **because** they are injected through the skin or mucous membranes.
- Parenteral products may be injected into the vascular system, muscle, or soft tissue to provide a **systemic action**, or into an anatomical space such as a joint or into a particular organ to provide a **local action**.
- These products should be sterile because they are placed inside body fluids or tissues, where infection can easily arise.

Parenteral Administration

- Parenteral preparation may be given by various routes:
- Intravenous (IV).
- Intramuscular (IM).
- Subcutaneous (SC.).
- Intradermal (ID).
- Intraperitoneal (IP).

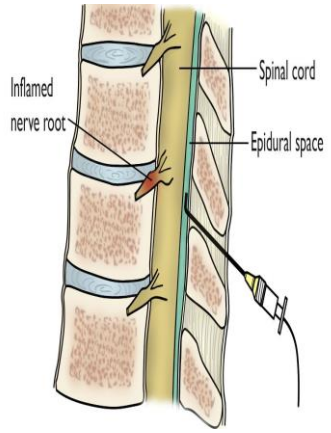


- After IV injection, the drug will be immediately available and **no need for absorption.**



Parenteral Administration

- All other routes, at least a blood vessel wall, and usually one or more tissue cell walls, must **be permeated before** the drug can enter the circulation.
- For non vascular injection, absorption is affected by factors such as the:
  1. Size and number of **blood vessels** supplying the tissue.
  2. The **movement** (exercise) of the tissue following injection.
  3. Physical and chemical **properties of the drug**.
  4. **Characteristics of the dosage form** as whether it is a solution, suspension, or emulsion; the nature of the vehicle, and pH,
- Once the drug in blood the drug distribution is affected by degree of protein binding and elimination rate by hepatic metabolism and/or renal excretion.



Parenteral Administration
General Notes

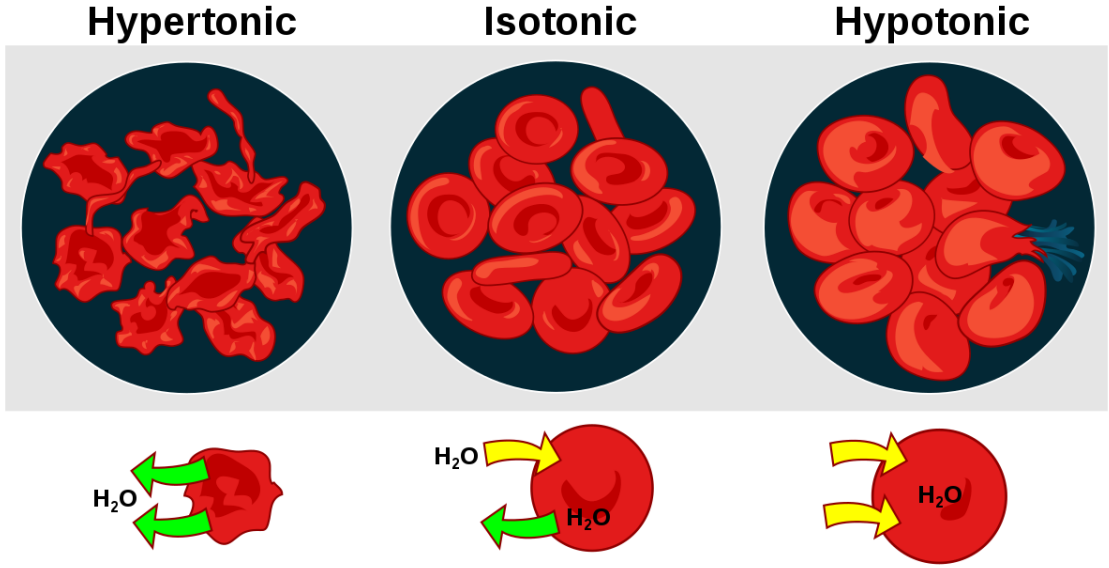
- IV and intraspinal preparations are given in form of **aqueous solutions** (no big particulate matter or oil droplet are allowed due to the risk of stroke).
- However, there are some **emulsion** preparations has been designed to be administered **via IV** (such as intralipid) in which the particle size are carefully controlled.
- IM, SC or ID preparation can be in form of **solutions, susp. or emulsions**.
- Intraocular preparation are not set to be injected, however they have to be sterile because they will be in contact to a body part that is easy to get infected.

Effect of Route of Administration

- The route if administration has effects on the properties of the parenteral formulations as follow:
- The **volume** of the dose allowed:
  1. The **intradermal** injection volume should be less than **0.2 ml** because tissue volume is small. And the absorption is quite slow owing to lack of blood vessels.
  2. **SC.** Injection should be **1 ml** or less.
  3. **IM** injections, it will be difficult to inject volumes larger than **2** ml. (it is ok to be larger but it will be difficult and for example painful)
  4. **Intraspinal injections** could be **10** ml or less.
  5. **Only for IV** administrations large volume are allowed (with careful control of the rate of administration). Usually not more than **one liter** at a time

Isotonicity

- Isotonicity related to the state of being isotonic, or having equal tension or tonicity.
- Isotonicity occurs in a cell when its solute concentration is the same as the solute concentration of the environment surrounding the cell.
- The result is there is **no net movement** of the water and permeable solutes.
- Example inside and outside red blood cells



Effect of Route of Administration

- **Isotonicity** is of great importance (why parenteral should be isotonic):

1. The most important one especially for intraspinal injection because the circulation of the cerebrospinal fluid is slow, and disturbances of osmotic pressure quickly cause headache and vomiting.
2. For ID injection which is mostly used for diagnostic purposes ➔ non isotonic solution may **give false results**.
3. For IM, SC injection: it is preferable for IM injection to be isotonic for **patient comfort**. But it is not necessary for these injections to be isotonic.
    - In addition, slightly hypertonic IM solution may have **higher** absorption.
4. **IV fluid** should be isotonic, however, slightly hypertonic solution may be given safely by slow administration rate.
5. Ophthalmic preparations should be isotonic because eye is also **sensitive** for **irritation** caused by non-isotonic solutions.

Ophthalmic Preparations

- These are product to be instilled onto the eye, they are non parenteral by definition but they have the same characteristics.
- They requires to be:
- Sterile (free of microbial contaminations).
- Highly pure.
- Have proper pH (buffer should be added to keep the correct pH range).
- Isotonic.
- Free of pyrogens (not highly recommended since pyrogen does not systemically absorb through the eye).

Long Acting Product

- These formulations are designed to provide slow, constant, and sustained released of a drug over a prolonged period of time.
- Has advantage over continuous IV infusion.
- The mechanisms for formulation such dosage forms are:

1. Formulating the drug as a **salt of very low solubility**.
2. **Controlling of particle size** can allow controlling drug dissolution, in which larger particle dissolve slowly.
3. **Binding the drug to adsorbents** → only free portion of drug will be available for absorption.
4. **Encapsulating drug** in a biodegradable macromolecules such as gelatin, phospholipid which will form a matrix from which the drug releases slowly.
5. Esterifying drug molecule which will deposit in the tissue at the injection site to form a reservoir of a drug.

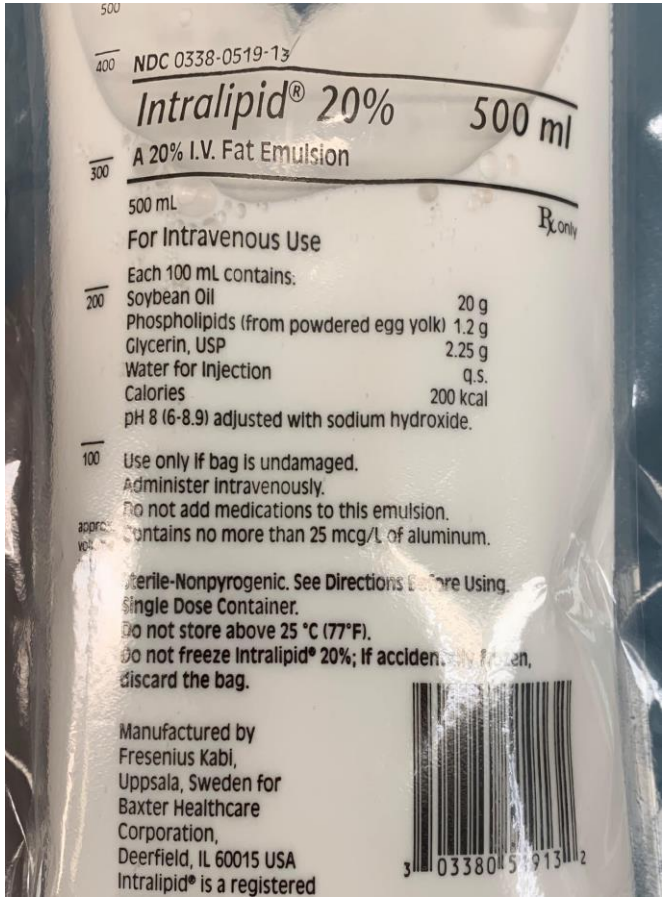
Parenteral Suspensions

- Properties of Parenteral suspensions:

1. The **amount of solids** can range between 0.5-5 %.
2. The **viscosity** should be limited due to the syringability.
3. The most important requirements is a small and uniform **particle size**. This is necessary for:
   a. **Slow, uniform** rate of **sedimentation** and predictable rates of dissolution and drug release.
   b. **Reduce** the tendency for **larger crystal** growth during storage.

Parenteral Emulsion

- Emulsion is a **mixture of oil and water** plus emulsifying agent.
- It is oil in water type (O/W) in which the oil is dispersed as small droplet (**internal phase**) inside the water medium (**external phase**).
- The **main concern** in parenteral emulsion type is to formulate and maintain **uniform oil droplet** within the **size range of 1-5µm** in size as the internal phase.
- This requirement makes the formulation of parenteral emulsion is **difficult**.
- This difficulty increased by the limited number of emulsifying agents available to be safely used parenterally.
- A third difficulty is to **protect the** oil phase form rancidity.



Parenteral Dosage Form Composition

- Active ingredient(s)
- Vehicle (solvent or solvent system)
- Solute(s)
- Package

Vehicle or Solvent System

- Most important vehicle for sterile products is **water** (vehicle for all natural body fluids).
- Solvent system (mixture of solvents) may be used to achieve target solubility
- Solvent systems suitable for sterile products limited for the products with little or no tissue irritation like water.
- **Tests for quality and purity of water:**

1. **Gravimetric evaluation** (measure total solid contents of dissociated and undissociated organic and inorganic substances). (isolation of materials and determination of amount by precipitation).
2. **Electrolyte measurement** of conductivity of water (conductivity indicate presence of microbes).
   - This test should be **zero Ohm** because we are using deionized water for preparations → if there is a conductance ➔ there should be a contamination.

Non-aqueous solvents

- Used in sterile pharmaceutical products because of hydrolytic reactions and solubility factors in which we need to remove the water entirely from the formulation.

- Properties of non-aq. solvents: **non-toxic, non-irritating, non-sensitizing and no adverse effect** on the ingredients of formulations.

- Example: solvents **miscible** with water (PEG 400 & 600, glycerin and propylene glycol). Solvents **immiscible** with water (fixed oils).

Solutes
Materials Other than the Active ingredient(s)

- **Added substance (enhance stability of products)**
- (solubilizers, antioxidants, chelating agents, buffers, tonicity contributors, antibacterial agents, antifungal agents, hydrolysis inhibitors and antifoaming agents).
- **Properties**:

1. Should be **non adversely affect** the products.
2. **Not interfere with therapeutic efficacy** or assay of active ingredients
3. **Non-toxic i**n quantity administered to patients.
4. They must be present and **effective throughout the useful life** of the product.
5. **Physical and chemical purity** (free of microbial and pyrogenic contaminants).

Solutes
1- Antibacterial agents

- Antibacterial agents at **bacteriostatic conc**. must be included in:

1. The formulation of product packaged in **multiple dose vial**.
2. In formulations to be sterilized or made by **aseptic manipulation**.

- Example is benzalkonium chloride in max. concentration of 0.01% and benzyl alcohol in conc. 0.5-10 %.
- **Source of contamination:**
- **People** (most common).
- **Air supply** (heating and cooling systems).
- **Infiltration** (particle comes through doors and windows).
- **Internal** (ceiling, walls, equipment, packaging).

Solutes
2- Antioxidants

- Protect therapeutic agents from oxidation particularly under accelerated conditions of thermal sterilization. They act in many ways:

1. **Reducing agents** (preferentially oxidized themselves → competing with the active ingredients for oxidation). In this case they are **consumed by time**.
2. **Blocking agents** (blocking oxidative chain reaction). In this case they are **not consumed**.
3. **Synergist compounds** (increase antioxidants).
4. **Chelating agents** (complex with catalysts that accelerate oxidation reactions).
   - Example: **ascorbic acid** (**reducing** agent) in conc of 0.02-0.1 %, **tocopherol (vit E)** as **blocking** agent in conc of 0.1-0.15 %.

- **Note**:
- In some product specially biopharmaceuticals, to reduce oxidation, oxygen (air) in the vial is replaced by inert gas.
- Combination of these agents are sometime used.


*VISINE® TEARS® Dry Eye Relief "Natural Tears Formula" contains 10 important ingredients found in your own natural tears.
Drug Facts
Active ingredients Purpose
Glycerin 0.2% Lubricant
Hypromellose 0.2% Lubricant
Polyethylene glycol 400 1% Lubricant
Uses
• for the temporary relief of burning and irritation due to dryness of the eye
• for protection against further irritation
Warnings
For external use only
When using this product
• remove contact lenses before using
• do not use if this solution changes color or becomes cloudy
• do not touch tip of container to any surface to avoid contamination
• replace cap after each use
Stop use and ask a doctor if
• you feel eye pain
• changes in vision occur
• redness or irritation of the eye lasts
• condition worsens or lasts more than 72 hours
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.
Drug Facts (continued)
Directions
• put 1 or 2 drops in the affected eye(s) as needed
• children under 6 years of age: ask a doctor
Other information
• store at 15° to 25°C (59° to 77°F)
Inactive ingredients
ascorbic acid, benzalkonium chloride, boric acid, dextrose, disodium phosphate, glycine, magnesium chloride, potassium chloride, purified water, sodium borate, sodium chloride, sodium citrate, sodium lactate
Questions?
call toll-free
888-734-7648 or
215-273-8755 (collect)
Caution: Do not use if VISINE® imprinted neckband on bottle is broken or missing.
Sterile
Visine®
TEARS®
DRY EYE
Relief
LUBRICANT EYE DROPS
KEEP OUT OF REACH OF CHILDREN
READ WARNING LABEL
Sterile
Visine®
TEARS®
DRY EYE
Relief
LUBRICANT EYE DROPS
Natural tears formula*
Moisturizes + soothes
1/2 FL OZ (15mL)
Dist: Johnson & Johnson Healthcare Products Division of McNEIL-PPC, Inc., Skillman, NJ 08558 USA Made in Belgium © McNEIL-PPC, Inc. 2014 www.visine.com
LOT:
EXP:
Sterile
Visine®
TEARS®
DRY EYE
Relief
LUBRICANT EYE DROPS
Protects against irritation
0 74300 01067 0
USA
995288
841

Solutes
3- Buffers

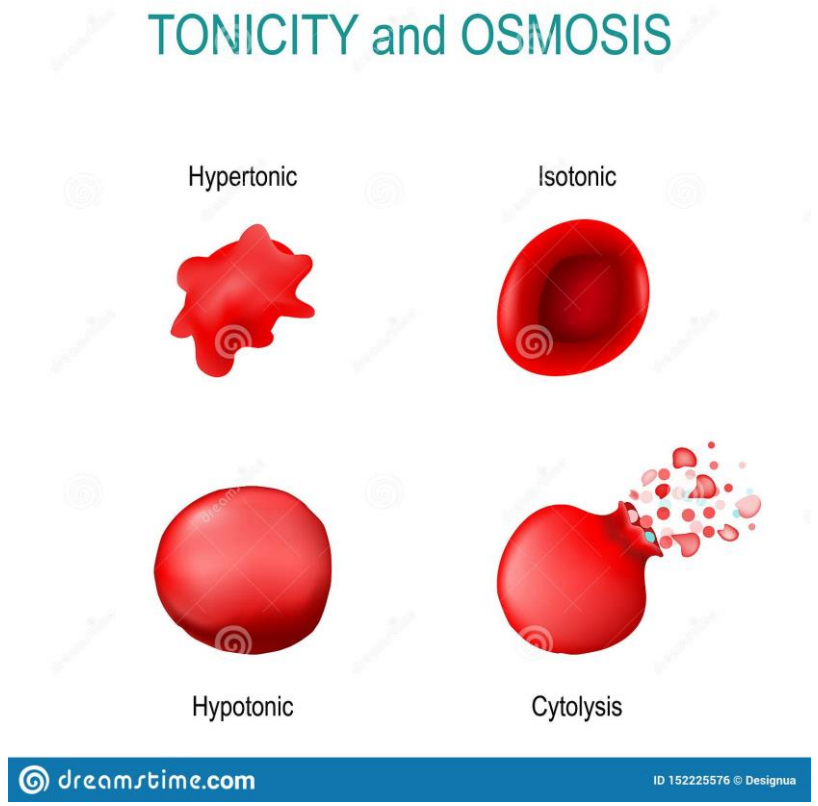
- like Acetate, citrate and phosphate buffers.
- **Maintain required pH** as the change in pH may cause significant alteration in the rate of degradative reactions.
- **Change in pH result from:**

1. **Dissolving glass** constituents in the product.
2. **Release of constituents from rubber** closure or plastic components in contact with the product.
3. **Dissolving of gases and vapors** from the airspace in the container and diffusion throughout the plastic or rubber component.
4. **Reaction within the product.**

- **Note**: buffers should have the capacity to maintain the **pH inside** the container but should be **easily overwhelmed** by bodies fluids after administration.

Solutes
4- Tonicity contributors

- Compounds that contribute to the isotonicity of a product to **reduce pain** of injection in areas with nerve endings.
- **Buffers** serve as tonicity contributors as well as stabilizers for the pH.
- Other tonicity adjuster is NaCl (electrolyte), glycerin (non-electrolyte).
- These materials are the **last ingredient** added to the formulation after other ingredients after the osmolality of the formulation has measured.



Solutes
4- Tonicity contributors

- **Methods of determination of isotonicity:**

1. **Freezing point depression.**
2. **Permeability of a living** semipermeable membrane that separate the solution from biologic cell system. This membrane is red blood cell membrane. → solution will be tested for any hemolytic reaction.

- If solution is hypotonic → tonicity adjuster is added.
- If solution is hypertonic:
- The degree of hypertonicity and route of administration need to be reconsidered. →

1. Choose **another route** of administration.
2. **Dilute** the formulation (if possible) or,
3. **Dilute** prior to administration.

Containers

- General notes:
- They are important because they are in direct contact with the products.
- **No** container presently available is **totally nonreactive**, particularly with aq. solutions.
- Physical characteristics are the primary consideration in selection of a protective container.
- **Glass containers** are commonly used for sterile product and interest in plastic container has been increased especially for ophthalmic preparations.

1- Plastic containers

- Plastic containers for medical field consist of:
- **Thermoplastic polymer** (soften by heat) but most of them stands normal autoclavable.
- Some containers also contain **other ingredients** such as: Plasticizers, Fillers, Antioxidants, Antistatic agents.
- Mainly used **because** (light in weight, low toxicity, non-breakable, low reactivity with the products (if they contain low amount of additives).
- Most commonly used plastic material is polypropylene and polyvinyl chloride (IV bags) which are:
  - Withstand normal autoclave.
  - A special advantage for plastic IV bag is that no air need to be enter as the liquid flows out, the bad simply collapses.

2- Glass containers

- Glass is a preferred containers for injections.
- The original and most stable is the one that made of silicon dioxide only **but its brittle → modified** with oxide such as boron, iron, and calcium to make it better.
- Two glass types available: (soda-lime and borosilicate).
- Care should be taken to test the effect of glass containers on formulation because content may migrate to solution by time and **may raise the pH of the formulation or catalyze reactions.**

2- Glass containers

- **Preferred Physical characteristics (Advantages):**

1. Can be used for **protection** of product from UV-light by using amber glass containers (made from iron oxide).
2. **Sufficient physical strength** to withstand high pressure during autoclaving, shipping, processing and storage.
3. **Low Thermal expansion** to withstand thermal shocks during washing and sterilization.
4. **Transparency** to facilitate inspection of the contents.
5. **Uniform physical dimensions** to facilitate handling by machines in automatic operations.

Rubber Closure

- Used to seal the openings of vials, bottles.
- Providing a material soft and elastic enough to permit entry of a hypodermic needle without loss of integrity of the sealed container.
- Non-reactive with the products in contact.
- It composed from variety of ingredients such as rubber (latex, the main component), synthetic polymer, sulfur, zinc oxide, carbon black filler and other component.
- **No ideal and perfectly** compatible closure is exist → compatibility should be **tested carefully**.

Rubber Closure

- **Two main Compatibility problems exist:**

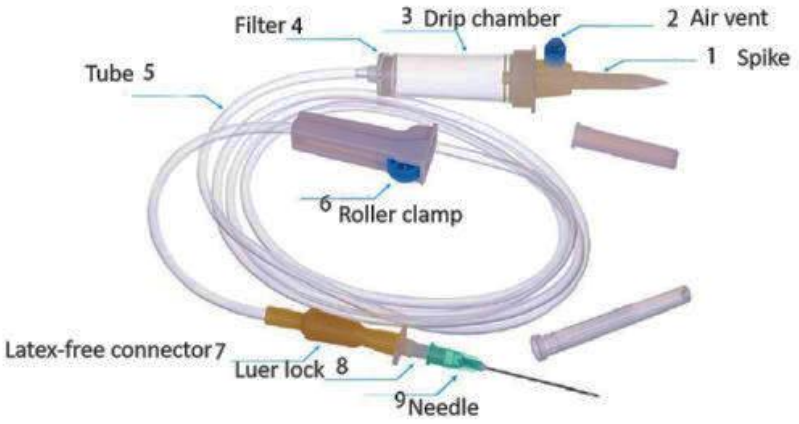
1. **Leaching of ingredients from rubber** with subsequent reaction with the product.
2. **Removal of ingredients** from the product by **sorption** or by vapor transfer through the closure.

- **Good rubber stopper should be:**

1. Elastic enough to snug fit on glass vial edges.
2. Spring back to close the hole made by the needle.
3. Must not produce large number of fragments as the hollow needle cuts through the stopper **(no coring and fragmentation).**
4. Should not permit the **easy transfer** of water vapor and gases in either direction.

Devices

- Items used to convey of products from container into the body or from one container to another.
- Although the contact time with the product is short but compatibility between product and device must be evaluated. Example insulin is found to be adsorbed by PVC tubing
- **Examples on Devices:**
- Hypodermic needles (stainless-steel).
- Plastic irrigating solution bottles.
- Plastic ophthalmic dropping bottles.
- Transfer needles.
- Transfer set (I.V. catheter from silicone rubber and nylon).



- All device components must **be visible clean** and fluid path through the device must meet the same rigid standards for cleanliness as the product.

Production of Parenteral Products

- Control of production involve controlling all the steps of production such as facilities, material, storage, and personnel.
- Production include creating of **SOPs** (Standard Operation Procedures): include writing all the steps that have been tested to be successful and no changes to SOPs are permitted without full testing.
- **Two main terms in production:**

1. **Quality assurance (prevention)**: include the **pre-planning** of those factors that affect the quality of the product and this is a preventative development process.
2. **Quality control (detection)**: concentrates on those **operations and test** that have been designed to evaluate the quality actually achieved in a product.

Production of Parenteral Products

- The production diagram is shown in the figure The formula is mixed and processes then filtered and transferred into aseptic filling room then packaging and to storage area.
- Al equipment need to be cleaned very well and sterilized if possible and depyrogenized.

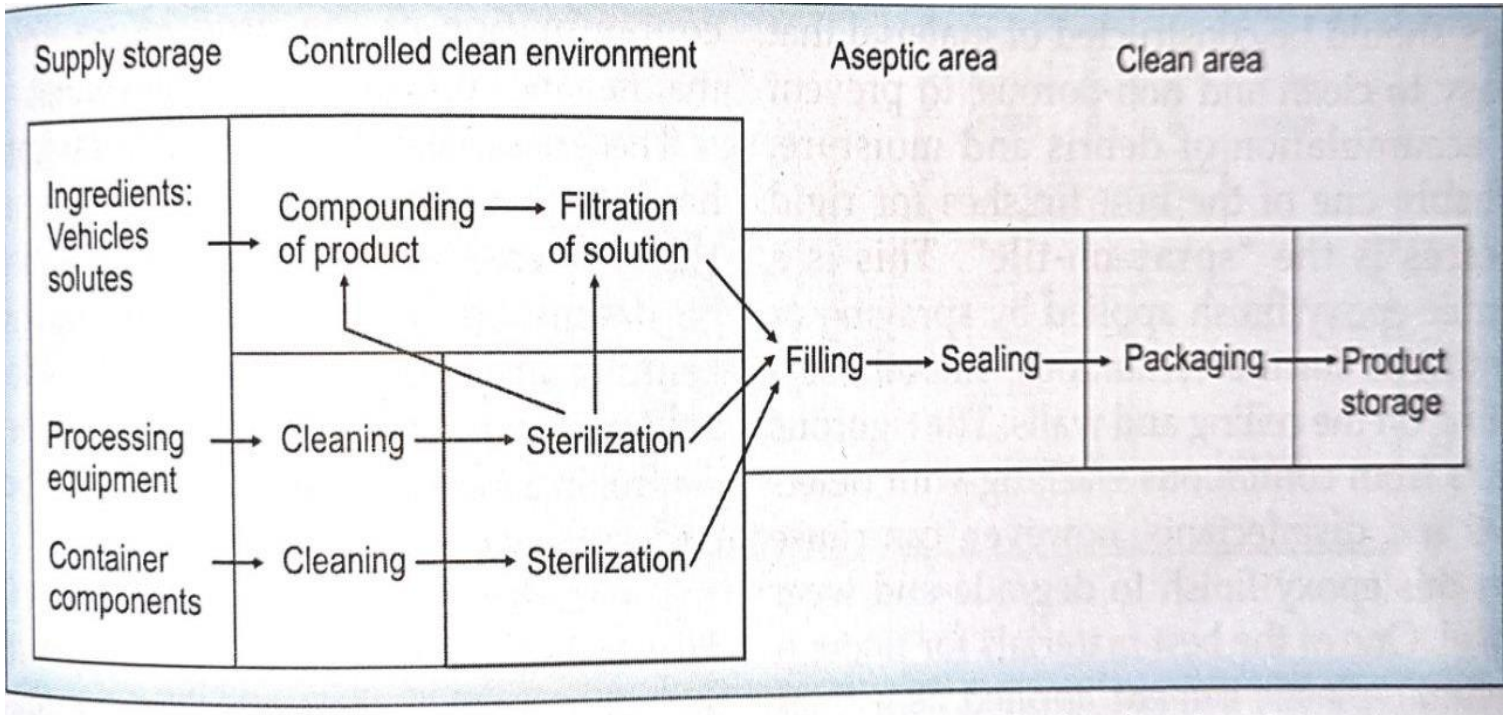


Fig. 23.3: Diagram of flow of materials through the production department

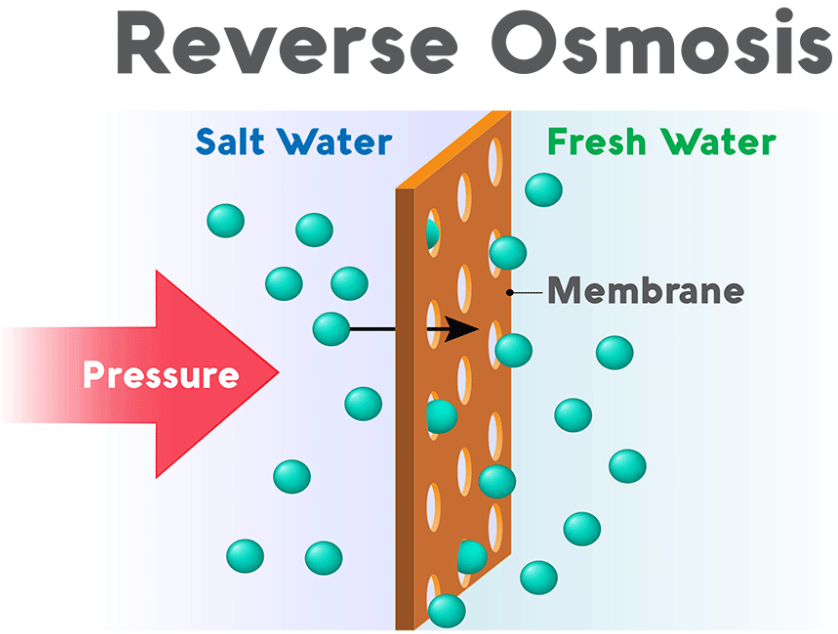
Processing
Water for injection

- Prepared by distillation and nowadays is prepared by **Reverse osmosis** which is approved by USP.
- **To get best water quality from distillation:**

1. **Pre-purification** of water by (deionization or filtration) to improve the quality of distillate and reduce the frequency of required cleaning due to insoluble extent in boiler.
2. **Removal of some contaminants** from vapor before condensed (by passage through an efficient baffle (filter) system.
3. **Ejection of volatile** constituents from top of the system before vapor is cooled to prevent from redissolve and appear in the condensate.
4. **Construction of all surfaces** that contact with vapor and condensate of a material that will not dissolve in even trace amount such as (304 stainless steel, **borosilicate glass**).

Reverse Osmosis System

- Functions by applying pressure (200- 400 psi) to raw water sufficient to force permeation of water through a select semipermeable membrane in **opposite** direction from natural osmosis.



- Commonly used membrane such as (cellulose ester or polyamides [nylon] which retain all macromolecules (including pyrogen) and small ions (Na^+ and Cl^-).

- Greater efficiency and reliability achieved by passing the water through 2 membranes in series.

Rinsing New Containers

- Cleaning new glassware without detergent treatment (because of the risk of detergent residue). The cycle is essentially rinsing process.
- To loosen debris by rinsing: alternating hot (clean steam) and cold treatment should be used.
- Final rinses should be done with filtered water for injection).
- This should be done by using machines.

- After cleaning containers → containers are often removed from the rinser and placed in clean stainless boxes for sterilization under the protection of HEPA-filtered airflow.

Cleaning Rubber and Plastic Components

- Debris are accumulated at the surface of rubber and plastic materials from surface molding operation and from handling (attracted and held on surface by electrostatic forces).

- Washed by mechanical agitation in a tank of hot detergent solution (0.5% sodium pyrophosphate) followed by a series a thorough water rinses , the final rinses being WFI.

Compounding of the Product

- **Filtration of solutions:**
- **Primary objectives** of filtering solutions are **clarification and sterilization.**
- **Clarification:** is termed polishing which is the removal of particulate matter down to at least **3 µm** size.
- **Sterilization:** further reduction in the size of the particulate matter removed, to approximately to **0.3 µm**. This will remove M.O. and spores.
- So, after clarification the solution is still **non-steril**e while after sterilization the solution is **clear and sterile**.
- solutions having high polish conveys the impression of exceptional quality and purity, highly desirable characteristics for a sterile solution.

Filling Equipment for Liquids

- **Filling machines** should have parts through which liquid flows that are **easy to clean and sterilize**.
- These parts also should be constructed of **non-reactive** materials such as borosilicate glass or stainless steel.
- Example: Syringes made from stainless steel when the pressures required for delivery of viscous liquids or large volumes while they are unsafe for glass syringes.

- Note: Sterile solutions of low potency dispense in large volume (up to 1L) **don't require precision of small volume** of potent injectables.
- So bottles of solutions are filled by **gravity, pressure or vacuum filling devices.**

Determination of Volume of Liquid in Container (USP Test)

- The total fluid volume that must be filled into a unit parenteral container is **typically greater than** the volume that would contain the exact labeled dose.
- This is required to **provide the loss that occur** at the time of administration due to adherence to the wall of the container and retention in the syringe and hypodermic needle lumen.
- There is a USP recommended excess volume table ➔
- To test volume of IV injection there is a USP limit table for testing.

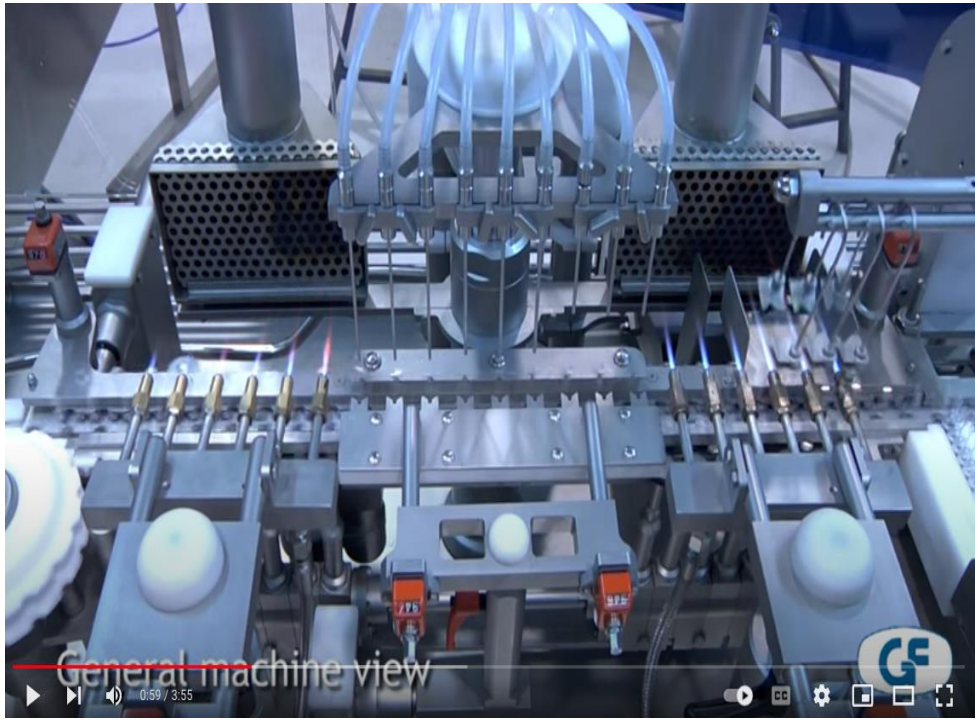
	Recommended Excess Volume	
Labeled Size	For Mobile Liquids	For Viscous Liquids
0.5 mL	0.10 mL	0.12 mL
1.0 mL	0.10 mL	0.15 mL
2.0 mL	0.15 mL	0.25 mL
5.0 mL	0.30 mL	0.50 mL
10.0 mL	0.50 mL	0.70 mL
20.0 mL	0.60 mL	0.90 mL
30.0 mL	0.80 mL	1.20 mL
50.0 mL or more	2%	3%

Not for Save

Label Volume	Number of unit to be tested
3 ml or less	At least 5 units
More than 3 ml	3
10 ml or more	At lest 1 unit

Filling Equipment for Liquids

- Filling machines for small volume should provide **precise filling**.
- Usually obtained from the strike of the plunger of a syringe.
- The stroke of these syringe forces the liquid through a tow-way valve that provides for an alternate filling the syringe from a reservoir and delivery to a container.
- Usually filling machines is **combined to a sealing machine** at the same time.
- Some machines also contains a washing and drying machine connected to the filling machine.



https://youtu.be/D-5dhRXtPBE

Filling equipment for Large Volumes

- **Note:** all of the following equipment **do not provide precision** level required for small volume drugs.

1. **Gravity filling machine**:
   - The liquid reservoir is positioned above the filling line with a hose connection from the reservoir to a shut-off device at the filling line.
   - Filling speed is slow but depends on simple principle.
2. **Pressure pump filler**:
   - Differ from gravity filler in that the liquid is under pressure.
3. **Vacuum filling machine**:
   - Used for faster filling line of large volume.
   - Vacuum is produced in the bottle and draw liquid from reservoir.

https://youtu.be/xRh4YBSQ81k
Pressure filling Machine

Quality Control

- Three common areas for quality controls include:

A. Incoming Stock:

1. Pyrogen test on WFI.
2. Glass tests on containers.
3. Identity test on rubber closure.
4. Microbial load test to determine number and type of M.O. present.

B. Manufacturing (processing):

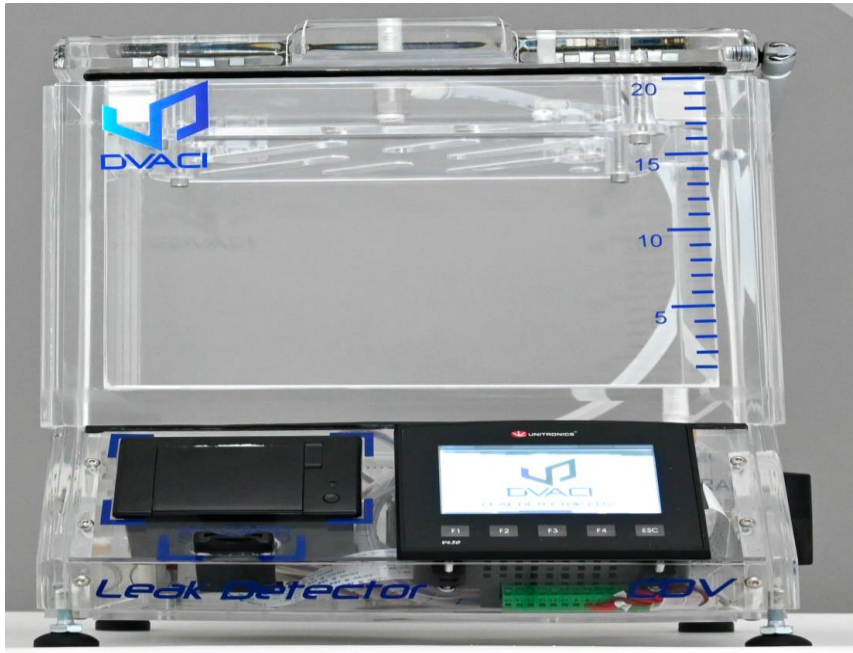
1. **Conductivity** measurement during distillation of WFI.
2. **Conformation of volume** of fill in product containers.

C. Finished product

1. Leaker test.
2. Clarity test.
3. Sterility test.

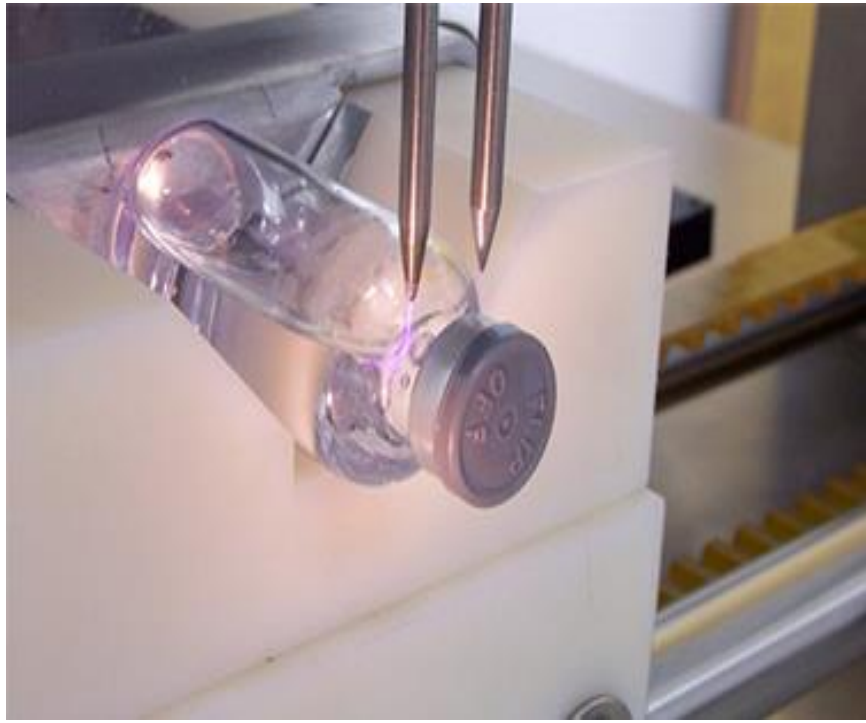
Leaker test

- Intended to detect incompletely sealed ampoules (having capillary pores or tiny cracks).
- M.O. or dangerous contaminants enter ampoules or contents may leak to the outside and spoil the appearance of package.
- **Detection of leaks by**:
- **For ampoules**:
- **Dye method**: applying a negative pressure usually in a vacuum chamber while the ampoule is entirely submerged in deeply colored dye solution (usually 0.5-1% methylene blue dye) so if dye penetrate then leak is present.



Leaker test

- Dye method can be done during autoclave cycle → doing both leak test and sterilization at the same time.
- **Note**: capillaries of 15 Micron or smaller may not be detected.
- **Note**: This test is not doing for vials because the rubber closure is not rigid.
- **For Bottles and vials**: these are vacuumed before closing. ➔
- **Spark tester probe** (moving from liquid layer into air space). blue spark occur if airspace is still evacuated.



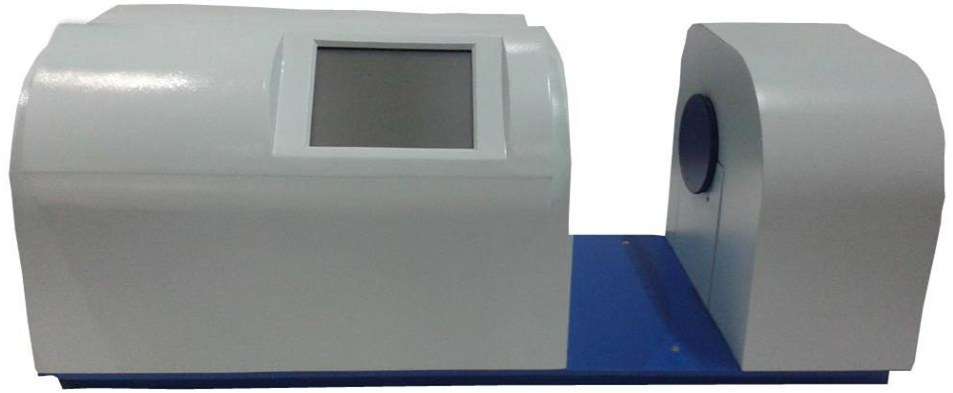
Clarity Test

- **Subjective** evaluation of the observer because it is done manually.
- Sterile products should be free from visible particulate ranging from 30 to 40 µm and larger in size.
- **Visual inspection** include (clean container, good light, baffled against reflection into eyes and viewed against **black and white background**, with contents motion with a **swirling action**).

Clarity Test

- **Note:**

1. **Moving particles** are easy to see than one that is stationary, but care to avoid introducing air bubbles which are difficult to distinguish.
2. **For detection of heavy particles:** invert the container as the final step inspection.



- Instrument available that uses the light scattering technology. (this one for inspection of **sample product and not the whole batch).**

Pyrogen Test

- Pyrogens are toxins produced by gram negative bacteria thar cause fever, chill, body aches in human.
- The presence of pyrogenic substances in parenteral preparations is determined by:
- **In vivo test**: a qualitative biologic test based on fever response in rabbits.
- **In vitro test**: utilizing gelling property of the lysate (LAL limulus amebocyte lysate).
- In the presence of pyrogenic endotoxins from gram –ve bacteria, a firm gel is formed within 60 min. when incubated at 37◦C.

- Note: A- LAL test is 5-10 times more sensitive than rabbit test.

Packaging

- Packaging of sterile products to convey for the user the quality, purity and reliability of the product and representing:
- **Dignified.**
- **Neat.**
- **Attractiveness.**
- **Accurate and completely** provide with information for its use.
- **Protect the product** against physical damage during shipping, handling and storage and from UV radiation (for light sensitive substances).