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# A Review: Basic Introduction of Parenterals Products

**Shagun Sharma[1], Aanchal Gwari[2], Baldev Singh[2], Himani Singh[2]**

**Department of Pharmaceutics, Gyani Inder Singh Institute of Professional Studies**

**Near Malsi Deer Park Road, Dehradun**

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**Corresponding author: Shagun Sharma**

## ABSTRACT

The term Parenteral derived from Greek words "Para" means outside & "Enteron" means intestine. The term "parenteral" used for any drug / fluid whose delivery does not utilize the alimentary canal for entering into body tissue. Parenterals are sterile solution/suspension of drug in aqueous or oily vehicle. Parenteral drugs are administered directly into the veins, muscles or under the skin, or more specialized tissues such as the spinal cord. Parenteral preparations are supplied in glass, plastic container and prefilled syringes with closures are made up of plastic or elastomer. The formulation of parenteral products involves the combination of one or more ingredients with a medicinal agent to enhance the convenience, acceptability, or effectiveness of the product. The most effective route for the delivery of the active pharmaceutical substances is the parenteral rout of administration, prescribed to unconscious patients. It was concluded that parenteral route of administration is the most effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs prescribed to unconscious patients.

The present study will outline the classification and types of parenteral products, route of administration, preformulation factors, formulation of parenterals, manufacturing of parenterals, evaluation of parenteral products, pyrogenicity, water for injection. It is more significant to produce good quality of parenteral. Parenterals are the pyrogen free liquids these are manufactured and stored according to GMP guidelines. Proper area environmental control, personnel observation will gives excellent parenteral products and attain their described therapeutic effect.

**Keywords:** Classification, Types, Routes of administration, Preformulation factors, Formulation, Manufacturing, Evaluation parameters, Pyrogenicity, Water for injection.,

## Introduction

The term Parenteral derived from Greek words "Para" means outside & "Enteron" means intestine. The term "parenteral" used for any drug / fluid whose delivery does not utilize the alimentary canal for entering into body tissue. Parenterals are sterile solution/suspension of drug in aqueous or oily vehicle. Parenteral drugs are administered directly into the veins, muscles or under the skin, or more specialized tissues such as the spinal cord. Parenteral preparations are supplied in glass, plastic container and prefilled syringes with closures are made up of plastic or elastomer (Reddy et al., 2013).

A drug administered parenterally is on injected through the hollow of a fine needle into the body at various sit and to various depths. The three primary routes of parenteral administration are subcutaneous, intramuscular, and intravenous, although there are others, such as intracardiac and intraspinal. Injections are sterile solutions or suspension of drugs in aqueous or oily vehicle ment for introduction into the body by means of an injectible needle under or through one or more layers of the skin or mucous membrane. Injection should be sterile, isotonic and free from foreign particles, such as dust, fibers etc. They must be introduced through the same route the same route for which they are planned. For example, an oily suspension meant for intramuscular injection may be very dangerous if it is administered by intravenous injections. Similarly, those strong drugs which are necessary to be given through

intramuscular injection may prove very critical if it is given by intravenous route (Mehtha et al., 2010). The parenteral preparations are free from the contaminating microorganism. Among these sterile dosage forms are the various small and large volume injectible preparations, irrigation fluid intended to bathe body wounds or surgical openings, and dialysis solutions. Biologic preparation,including vaccines, toxoids, and antitoxins. Sterility in these preparations is essential because they are placed in direct contact with the internal body fluids or tissues, where infection can easily arise (Parket al., 1999). Parenteral dosage form are those dosage form which drugs are directly injected into body tissue through one or more layer of skin and mucous. Injections are sterile, pyrogen free preparation intended to be administered parenterally. The term parenteral refers to the injectible routes of administration (Agarwal et al., 2012).

**Table 01: Categories and characteristics of parenteral**

| Categories of Parenteral Preparations | Characteristics of Parenterals |
|---|---|
| ● Injections or infusions<br>● Concentrates for injections or infusions<br>● Powder for injections or infusions<br>● Gels for infusions<br>● Implants | ● Sterile<br>● Particulate free<br>● Pyrogen free<br>● Stable for intended use<br>● pH not vary significantly<br>● Osmotic pressure similar to blood |

## HISTORY OF PARENTERALS

- **1657: Sir Christopher Wren -** First recorded injection in animals.
- **1855: Dr. Alexander Wood -** First subcutaneous injections of drugs using hypodermic needles.
- **1920s: Dr. Florence Seibert -** Proof of microbial growth resulting in infections.
- **1926:** Inclusion in the National Formulary.
- **1944:** Discovery of Ethylene Oxide(used for sterilization).
- **1946:** Organization of Parenteral Drug Association.
- **1961:** Development of Laminar Air Flow Concept.

## ADVANTAGES OF PARENTERAL ADMINISTRATION

- Fastest method of drug delivery.
- Viable alternative.
- Use for Uncooperative patients.
- Nauseous patients.
- Unconscious patients.
- Less patient control.
- For the patient who can have nothing by mouth.
- Prolonged action.
- Correcting serious fluids and electrolyte imbalance

## DISADVANTAGES OF PARENTERAL ADMINISTRATION

- Trained personnel.
- Pain.
- Difficult to reverse an administered drug's effects.
- Manufacturing and Packaging requirements.
- Costly.
- Needle sticks Injury

## CLASSIFICATION AND TYPES

**Guiding Principles For Simple Parenteral Solutions:**

**Selection of Injectable Volume:** Pharmacopoeias classify the injection into 2 types:

- **Small Volume Parenterals (SVPs):** These are usually 100ml or less. Depends on the intended use these are packaged in different ways.

- **Large Volume Parenterals (LVPs):** a single dose injection which intended for IV use and is packaged in containers, containing more than 100 ml (Thomas et al., 2018).

SVPs are usually given rapidly in small volume are called as a bolus. In LVPs also they added like 5% dextrose and 0.9 % sodium chloride injection or infusion is administered through IV infusion. Based on the pharmacokinetics of the drug the bolus or infusions are selected. A bolus administration is preferred for intramuscular or subcutaneous injections. Subcutaneous route is used if the injection volume is less than 1- 1.5 mL and through intramuscular route usually no more than 2 mL. In the formulation of a solution product, the main step is to select the administration volume and concentration (Joanne, 2015; Mitsuhashi et al., 1993).

**Table 02: Comparison between SVPs and LVPs**

| Small Volume Parenterals (SVPs) | Large Volume Parenterals (LVPs): |
|---|---|
| i) Requires little or no manipulation<br>ii) Extended stability<br>iii) Little wastage<br>iv) Do not offer flexibility in quantity/concentration<br><br>**Primary Uses of SVP**<br>a) Therapeutic injections<br>b) Ophthalmic products<br>c) Diagnostic agents including<br>i) Diagnostic radio pharmaceutical<br>ii) Allergenic extracts | i) Flexible but requires manipulation<br>ii) Used for maintenance or replacement therapy<br>iii) Free of preservatives<br>iv) Volume must not exceed 1L (except irrigation sols)<br><br>**Clinical Utilization of LVPs**<br>a) Basic nutrition<br>b) Restoration of electrolyte balance<br>c) Fluid replacement<br>d) Blood and blood products drug carriers |

**ROUTE OF ADMINISTRATION** (Aminov, 2010)

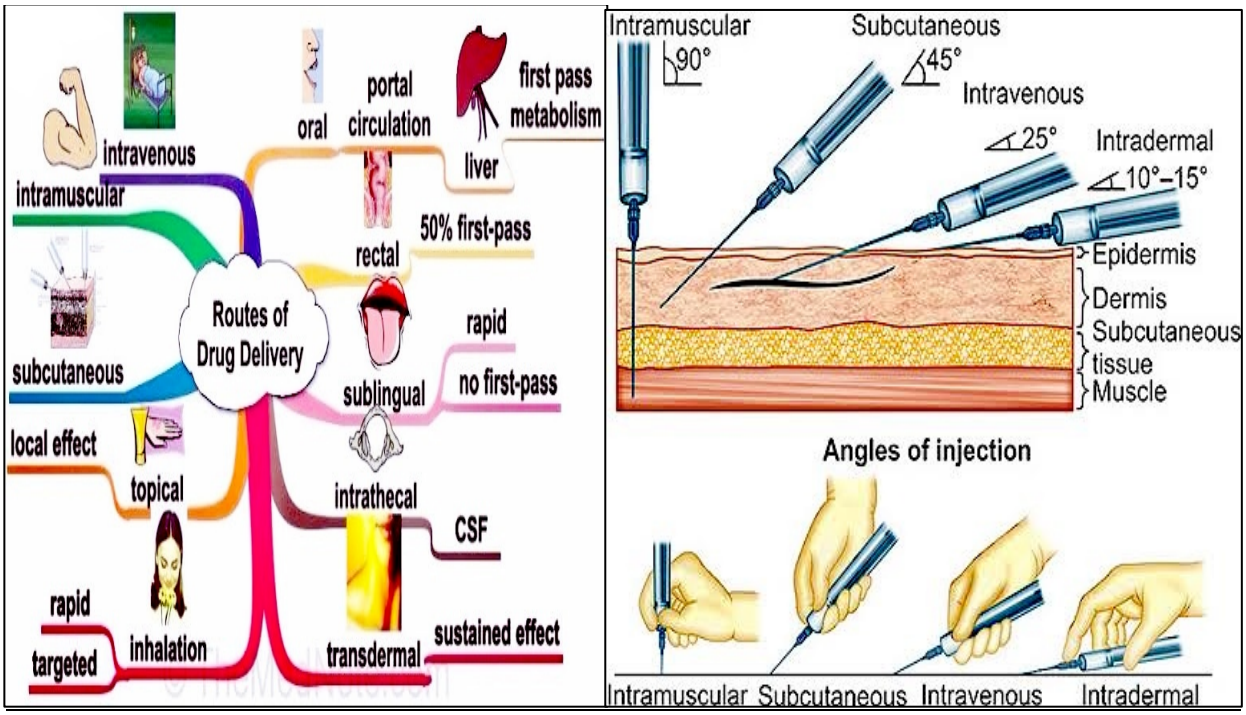



**Figure 01: Different routes of administration**

**1. Parenteral Route:** Routes of drug administration other than oral route are known as parenteral route. This refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa and subsequently liver.

**Advantages:**

i) Absorption is faster, hence drug can be administered rapidly and in accurate dose in time of emergencies.

ii) Gastric irritation and vomiting are not provoked.

iii) It can be employed in unconscious, uncooperative or vomiting patients.

iv) There are no chances of interference by food or digestive juices.

v) Liver is bypassed.

**Disadvantages:**

i) The preparation has to be sterilized and is costlier.

ii) The injection may be painful.

iii) Self medication is difficult - another trained person is required to give theinjection.

iv) Abcess and inflammation at the site of injection may take place.

**2. Intradermal Injection:** The drug is injected into the dermis of skin raising a bleb (e.g. BCG vaccine, sensitivity testing of drugs) or scarring / multiple puncture of the epidermis through a drop of the drug (small pox vaccine) is done. This route is employed for specific purpose only.

**3. Subcutaneous Injection:** The drug is injected under the skin. The drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves (irritant drugs cannotbe injected but is less vascular (absorption is slower).

**Advantages:**

i) Self injection is possible because deep penetration is not required.

ii) Oily solutions or aqueous suspensions can form a depot which will release drug slowly for a prolonged period.

**Disadvantages:**

i) Since skin is richly supplied by nerve-endings hence irritant drugs cannot be injected.

ii) This route should be avoided in shock patients. e.g. Insulin injection.

**4. Intramuscular Injection:** The drug is injected in one of the large skeletal muscles- deltoid, triceps, gluteus maximus, rectus femoris etc.

**Advantages:**

i) Muscle is less richly supplied with sensory nerves, hence mild irritants can be injected.

ii) Muscle is more vascular hence absorption is faster than subcutaneous route.

iii) It is less painful.

iv) Depot preparations can be injected by this route and the action of the drug may be prolonged.

**Disadvantages:**

i) Since deep penetration is needed hence self-medication is not possible.

ii) Large volume cannot be given. e.g. Low volume injections - Vitamin A, hydrocortisone acetate, tetanus toxoid, antibiotic etc.

**5. Intravenous Route:** The drug is injected as a bolus or infused slowly over hours in one of the superficial veins (generally brachial vein).

**Advantages:**

i) The drug directly reaches the blood stream and effect is produced immediately, hence, this route can be used in emergencies.

ii) The inside of the veins is insensitive and drug gets diluted with blood quickly, therefore, even highly irritant drugs can be injected intravenously.

iii) Large volumes can be infused (e.g. normal saline).

iv) It is useful in unconscious patients.

v) Desired blood concentration can be achieved.

**Disadvantages:**

i) Drugs that precipitate in the blood cannot be administered. Only aqueous solution can be administered.

ii) No drug can be given in depot form - so the action is not prolonged compared to other parenteral administrations.

iii) Untoward reactions if occur are immediate.

iv) Once administered, withdrawal of the drug is not possible.

**6. Intra-arterial Route:** A drug is injected into an artery. The effect of a drug can be localized in a particular organ or tissue by choosing the appropriate artery. Anticancer drugs are sometimes administered by this route.

**7. Intra-peritoneal Route:** In this route a drug is injected into the peritoneal cavity. By this route fluids like glucose and saline can be given to children.

**Table 03: Comparison of routes of parenteral administration**

| Characteristics | Subcutaneous Route | Intramuscular Route | Intravenous Route | | Intradermal Route |
|---|---|---|---|---|---|
| | | | IV injection (Vein puncture) | IV infusion (Venoclysis) | |
| **Site** | Beneath the skin in the loose intestinal tissue | Striated muscle fibres, 1.5 inches | Large proximal veins | Vein | Beneath epidermis, anterior forearm |
| **Volume** | 0.5 - 2 ml | 0.5 - 2 ml | 1 - 1000 ml | 100 - 1000 ml | 0.05 - 0.1 ml |
| **Characteristics** | Slower onset | Rapid onset, Drug depot | Extremely rapid and predictable response | LVP: to provide energy, water and dilution effect. Drug: provide continuous and prolonged | Detect hypersensitivity reactions |
| **Formulation** | Not irritating | Nearly all drug classes | Solutions, Emulsions, Liposomes | Solutions and some emulsions: normally need to be isotonic | Isotonic |
| **Precautionary Note** | Ensure that the needle is not in a vein | Potential muscular or neurl damage | Drug shocks: too rapid, control the injection rate | IV admixtures: must avoid incompatibility, sterility | Null |

## PREFORMULATION FACTORS:

Preformulation can be defined as study about physical & chemical properties of drug substance prior formulation. Various preformulation parameters are as follows:

**1. pH:** It can be determined by pH meter. The generation of pH/stability and pH/ solubility profiles is the main step in the selection of pH in a formulation. For the maximum physiological acceptability, the target pH is approximately pH 7.4. When the dosing through IV route, a wide pH range can be tolerated and a rapid dilution wit blood also can be achieve. pH value ranging from 2 to 12 can be tolerated in these situations when intramuscular administration is uses the

dilution rate is slower and it is further decreases when the subcutaneous route is administered. Tolerability of a formulation depends on its buffering capacity (Joanne, 2015).

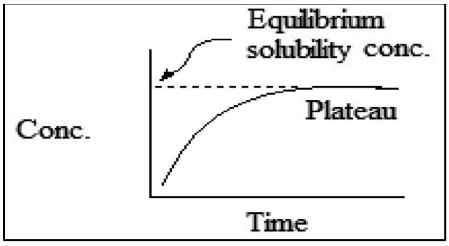
**Table 04: Buffers used in the approved parenteral products** (Thomas et al., 2018)

| Buffer | pH Range |
|---|---|
| Acetate | 3.8 -5.8 |
| Ammonium | 8.25 – 10.25 |
| Ascorbate | 3.0 -5.0 |
| Benzoate | 6.0 – 7.0 |
| Bicarbonate | 4.0 – 11.0 |
| Citrate | 2.1 – 6.2 |
| Diethanolamine | 8.0 – 10.0 |
| Tromethamine (TRIS, THAM) | 7.1 – 9.1 |

**2. SOLUBILTY:** The formulation must contain a co-solvent or a solute which sufficiently increases and maintains the drug in solution, if the drug is insufficiently soluble in the water at the dosage required. Solubility is the major factor that gives the concentration in the dosage form. A dispersed system dosage form developed, when simple formulation additives do not result in the solution (Linda, 2013).

**Determination of equilibrium solubility of a drug:** The drug is dispersed in a solvent. The suspension is agitated at a constant temperature. Samples of the suspension are withdrawn as a function of time, clarified by centrifugation, and assayed to establish a plateau concentration.

**Solvents Taken:**




- 0.9% NaCl at room temperature
- 0.01 M HCl at RT
- 0.1 M HCl at RT
- 0.1 M NaOH at RT
- At pH 7.4 buffer at 370C

**Drug concentration is determined by the following analytical methods**:

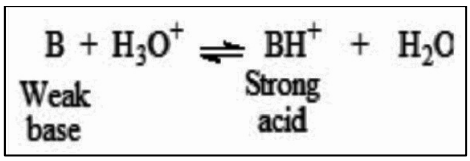
- HPLC
- UV –Spectroscopy
- Fluorescence Spectroscopy
- Gas Chromatography

**Solubility depends on:** pH, Temperature, Ionic strength, Buffer conc.

**3. pKa:** When a weakly acidic or basic drug partially ionizes in GI fluid, generally, the unionized molecules are absorbed quickly.

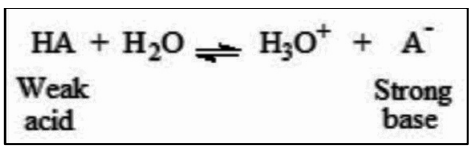
Handerson-Hasselbach equation provides an estimate of the ionized and unionized drug concentration at a particular pH.

**For acidic drug: e.g.**




**pH = pKa + log [ionised]/[unionized] = pKa + log [A-]/[HA] = pKa + log [base]/[acid]**

**For basic drug: e.g.**




**pH = pKa + log [ionised]/[unionized] = pKa + log [A-]/[HA] = pKa + log [base]/[acid]**

**Method of determination of pKa of a drug:**

- Detection of spectral shifts by UV or visible spectroscopy at various pH.

**Advantage:** Dilute aqueous solutions can be analyzed by this method.

- Potentiometric titration

**Advantage:** Maximum sensitivity for compounds with pKa in the range of 3 to 10.

- Variation of solubility at various pH.

**4. Compatabilty Studies: Differential Scanning Calorimetry**

In DSC method the difference in energy inputs (H) into a sample and reference material is measured as a function of temperature as the specimens are subjected to a identically controlled temperature programme.

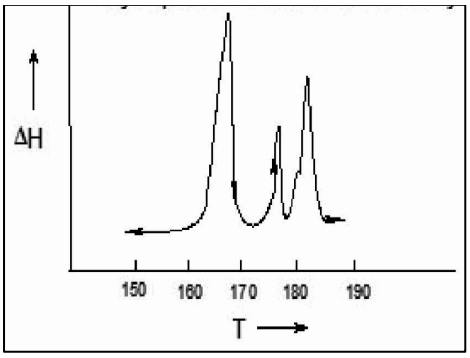



**Figure 02: Graph represents polymorphism of Phenobarbitone studied by DSC**

**Samples that may be studied by DSC or DTA are:** Powders, fibres, single crystals, polymer films, semi-solids or liquids.

**Applications of DTA / DSC in preformulation studies:**

- To determine the purity of a sample.
- To determine the number of polymorphs and to determine the ratio of each polymorph.
- To determine the heat of solvation.
- To determine the thermal degradation of a drug or excipients.
- To determine the glass-transition temperature (tg) of a polymer.

**5. PARTICLE SIZE:**

Particle size can be determined by any of the following method:

- Coulter counter: electrical sensing zone method HIAC – counter: optical sensing zone.
- Malvern particle & droplet sizer: Laser diffraction method.

**Procedure:** Samples prepared for analysis are dispersed in a conducting medium (e.g. saline) with the help of ultrasound and a few drops of surfactant (to disperse the particles uniformly). A known volume (0.5 to 2 ml) of this suspension is then drawn into a tube through a small aperture (0.4 to 800 m diameter) across which a voltage is applied. As each particle passes through the hole, it is counted and sized according to the resistance generated by displacing that particles volume of conducting medium. Size distribution is reported as histogram.

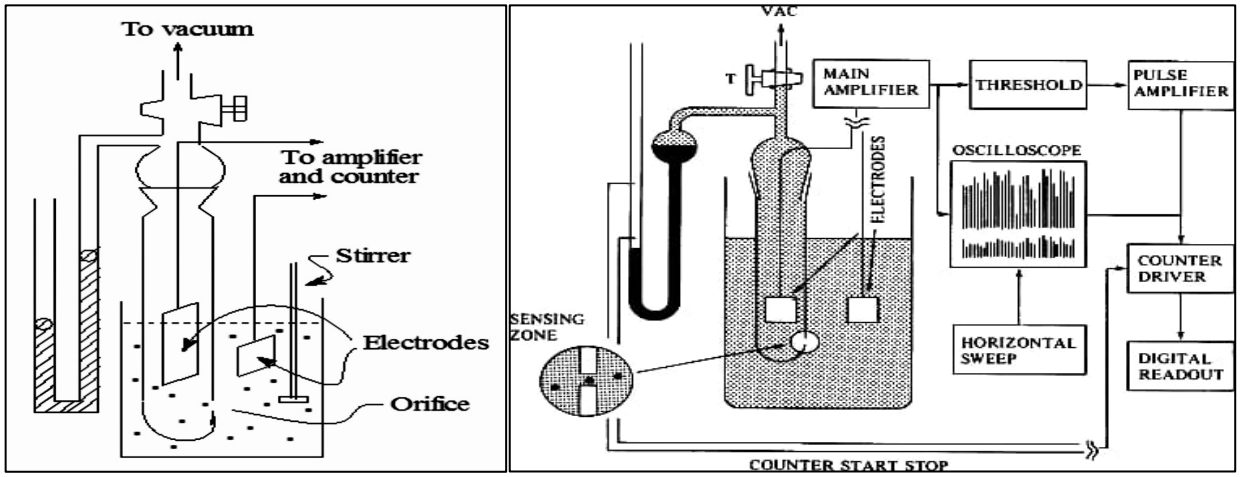



**Figure 03: Coulter counter apparatus**

**6. PHARMACOKINETICS OF DRUG:** The absorption rate for routes of administration other than intravenous or intra-arterial, distribution, metabolism and excretion of drugs have effect on route of administration that selected, based on the type of formulation. For example: a drug having a rapid pharmacokinetic profile, there is need of development of modified release dosage formulations. Pharmacokinetics also affects the drug dose and the dosage regimen (Linda, 2013).

**7. DRUG STABILITY:** If the drug possesses significant degradation problems in the solution, then freeze dried or sterile solid dosage form should be developed. Sometimes drug concentration affects the stability in turn, affect size and the packaging system used also. Stability determines the storage conditions since it indicates the drug expiration date (Linda, 2013).

## FORMULATION OF PARENTERALS

(Nussbaum et al., 2006)

**General guidance for developing formulations of parenteral drugs:**

The following factors should follows when a drug is given through parenterally rather than orally:

i) The onset of action of drug is mostly more rapid but the duration is short.

ii) Since the drug potency tends not to alter immediately by the liver or stomach, so the dosage form is often smaller.

iii) The cost for the therapy is higher (Thomas et al., 2018).

Parenteral drugs are formulated as Solutions, Suspensions, Emulsions, Liposome, Microspheres, Nanosystems and powders to be reconstituted as solutions. The formulation of parenteral products involves the combination of one or more ingredients with a medicinal agent to enhance the convenience, acceptability, or effectiveness of the product. Rarely is it preferable to dispense a drug singly as a sterile dry powder unless the formulation of a stable liquid preparation is not possible.

**Solvent System:** A parenteral therapeutic agent is given by preference as a solution. If aqueous, the solution is physiologically compatible with body tissues, and the biological response elicited should be reasonably predicted.

The high dielectric constant of water makes it possible to dissolve isonizable electrolytes, and its hydrogen bonding potential brings about the solution of such organic substances such as Alcohols, Aldehydes, Ketones & Amines. Water is a poor solvent for nonpolar compounds such as alkaloidal bases, which requires nonpolar solvents.

Adding to the complexity of solvent selection is the requirement that solvents to be injected must be of low toxicity to body tissue. Ether is a solvent for Testosterone, but is highly irritating to body tissue & cannot be used alone as a solvent for an injectable preparation. Frequently, the desired solubility can be achieved with mixed solvents, eg, the use of 40 % ethanol in water to solubilize the digitalis glycosides.

## EXCIPIENTS USED FOR PARENTERAL PRODUCTS

### 1. VEHICLES:

**A. Water Miscible Vehicles:** Primarily to effect solubility of drugs and/or reduce hydrolysis. Solvents that are miscible with water and that are usually used in combination with water as the vehicle includes: Dioxolane, Dimethylacetamide, N-(β-hydroxyethyl)-lactamide, Butylene glycol, Polyethylene glycol 400, Polypropylene glycol, Glycerine, Ethyl alcohol (Pankey et al., 2004; Lin et al., 2013).

**B. Non-aqueous vehicles:** In the formulation it is sometimes necessary to eliminate water entirely or in part from the vehicle, primarily because of solubility factor or hydrolytic reactions.

**Characteristics of Non aqueous solvents are as follows:**

- It must not be irritating, toxic or sensitizing.
- It must not exert an adverse effect on the ingredient of formulation.

- Water immiscible solvents include: Fixed oil, Ethyl oleate, Isopropyl myristate, and Benzyl benzoate.
- The most frequently used non aqueous solvents are Polyethylene glycol, Propylene glycol and Fixed oils. Fixed oils (Vegetable origin, liquid & rancid resistance, Unsaturated, Free fatty acid content). Eg, Peanut oil, Corn oil, Cotton seed oil, Sesame oil, Soybean oil, Ethyl oleate, Isopropyl myristate (Vaishya et al., 2014).

## 2. ADDED SUBSTANCES

**A. Antibacterial Agents:** Antibacterial agents in bacteriostatic concentration must be included in the formulation of products packaged in multiple dose vials, and are often included in formulations to be sterilized by marginal process or made by aseptic manipulation. They are mainly required to prevent micro-organism growth.

Eg., Phenyl mercuric nitrate & Thiomersal (0.01 %), Benzethonium chloride & Benzalkonium chloride (0.01 %), Phenol or Cresol (0.5 %), Chlorobutanol (0.25 - 0.5 %), Metacresol (0.1 – 0.25%), Phenylmercuric nitrate (0.001%), Propylparaben (0.005 – 0.035%), Methylparaben (0.01 – 0.18%) (Fleming, 1929; Moyer et al., 1946).

**B. Buffers:** Buffers are added to maintain a required pH for many products. A change in pH may cause significant alteration of the rate of degradative reactions.

**Change in pH may occur:**

- During storage as a result of the dissolving of glass constituents in the products.
- Release of constituents from rubber closure or plastic constituents in contact with the products.
- Dissolving of gases and vapors from the airspace in the container and diffusion through the rubber or plastic components.

**Most commonly employed buffers are as follows:** Sodium acetate (0.8 %), Lactic acid (0.1 %), Potassium phosphate (0.1 %), Acetic acid (0.22 %), Citric acid (0.5 %) Adipic acid (1.0 %), Sodium tartrate (1.2 %), Sodium citrate (4.0 %), Sodium benzoate & Benzoic acid (5.0 %).

**C. Antioxidants:** Antioxidants are mainly included to the formulation to protect a therapeutic agent susceptible to oxidation, and may function in at least two ways;

- **Reducing Agents:** They act by being preferentially oxidized (reducing agent) and thereby gradually used up. Eg, Ascorbic acid, Sodium bisulfate, Thiourea.
- **Blocking Agent:** They act by blocking an oxidative chain reaction in which they are not usually consumed. Eg, BHT, Tochopherol.

In addition some compounds have been found to act as synergists increasing the effectiveness of antioxidants, particularly those bocking oxidative reactions.

**D. Surfactants:** Included to solubilise the active ingredients. Eg, Polyethylene sorbitan monooleate. Sorbitan monooleate. Increase and maintain drug solubility. Examples include complexing agents and surface active agents. The most commonly used complexing agents are the cyclodextrins, including captisol. The most commonly used surface active agents are polyoxyethylenesorbitanmonolaurate (tween 20) and polyoxyethylenesorbitanmonooleate (tween 80) (Schatz et al., 1944).

**E. Tonicity Agents:** All parenteral products should be isotonic, especially osmolarities should target between 280 and 290 mOsm/L during a formulation. For LVPs isotonicity is very essential. Either the rapid dilution with blood that will occur after injection or prior to administration the product itself diluted with an LVP, a wider range of osmolarities can be tolerated in SVPs. For hypotonic solutions hypertonic solutions are preferred since the risk of haemolysis associated with the hypotonic solution. By the use of excipients the hypotonic solutions are avoided, since the sodium chloride to raise the osmolality. To avoid the tissue damage parenteral formulations should be isotonic with human plasma. Compounds contributing to the isotonicity of a product reduces the pain of injection in areas with nerve

endings. Buffers may serve as tonicity contributors as well as stabilizers for the pH.

Eg., Potassium chloride, Lactose (0.14 – 5.0 %), Mannitol (0.4 – 2.5 %), Sodium sulfate (1.1 %), Sorbitol (2.0 %), Dextrose (3.75 – 5.0 %) (Joanne, 2015; Pramanich et al., 2013; Raper et al., 1946).

**F. Chelating Agent:** Only a limited number of chelating agents are used in parenteral products. They serve to complex heavy metals and therefore can improve the efficacy of antioxidants or preservatives. disodium EDTA, citric acid, tartaric acid and some amino acids also can act as chelating agents.

Eg., Edentate disodium (0.00368 - 0.05 %), Edentate calcium disodium (0.04 %), Edentate tetrasodium (0.01 %) (Demain et al., 1999).

**G. Local Anaesthetic:** Procaine HCL (1.0 %), Benzyl alcohol (5.0 %).

**H. Stabilizers:** Sodium caprylate (0.4 %), Sodium saccharin (0.03 %), Creatinine (0.5 – 0.8 %), Glycine (1.5 – 2.25 %).

**I. Choice of Excipients:** In pharmaceutical products the formulations should developed by using excipients. In parenteral products the quality, particularly in microbial terms of excipients should be considered necessarily. The injectable grades are usually used for parenteral excipients which have strict bio burden and endotoxin limits. The excipients have pharmacopoeial grade also acceptable. But this is usually to apply In-House microbiological specification limits (Joanne, 2015). The integral part of pharmaceutical products development is excipients, to achieve the desired product profile (stability and efficacy) (Pramanich et al., 2013). Excipients are important to assure safety (antimicrobial preservatives) to minimize pain and irritation on injection and tocontrol or prolonged drug delivery (Michael, 2002).

## MANUFACTURING OF PARENTERALS

The productions are where the parenteral preparation are manufactured can be divided into five sections:

### 1. CLEAN-UP AREA:

- It is not aseptic area.
- The entire parenteral product must be free from foreign particles & microorganism.
- Clean-up area should be with stand moisture, dust & detergent.
- This area should be kept clean so that contaminants may not be carried out into aseptic area.

### 2. PREPARATION AREA:

- In this area the ingredients of the parenteral preparations are mixed & preparation is made for filling operation.
- It is not essentially aseptic area but strict precautions are required to prevent any contamination outside.

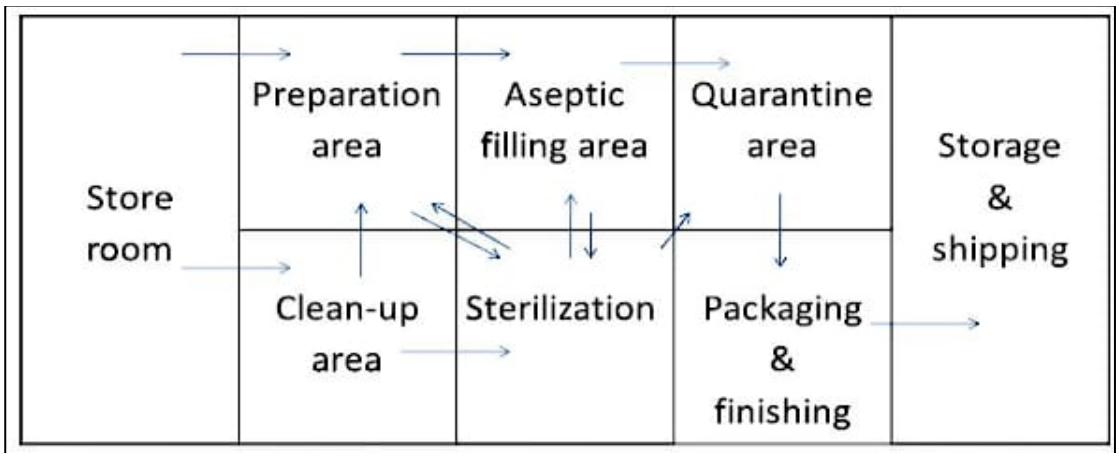



**Figure 04: Diagram represents preparation area in manufacturing of parenterals**

**3. ASEPTIC AREA:**

- The parenteral preparations are filtered, filled into final container & sealed should be in aseptic area.
- The entry of personnel into aseptic area should be limited & through an air lock.
- Ceiling, wall & floor of that area should be sealed & painted.
- The air in the aseptic area should be free from fibres, dust & microorganism.
- High efficiency particulate air filters (HEPA) is used for air.
- UV lamps are fitted in order to maintain sterility.

**4. QUARANTINE AREA:**

- After filling, sealing & sterilization the parenteral product are held up in quarantine area. Randomly samples were kept for evaluation.
- The batch or product pass the evaluation tests are transfer into finishing or packaging area.

**5. FINISHING & PACKAGING AREA:**

- Parenteral products are properly labeled & packed.
- Properly packing is essential to provide protection against physical damage.
- The labeled container should be packed in cardboard or plastic container.
- Ampoules should be packed in partitioned boxes.

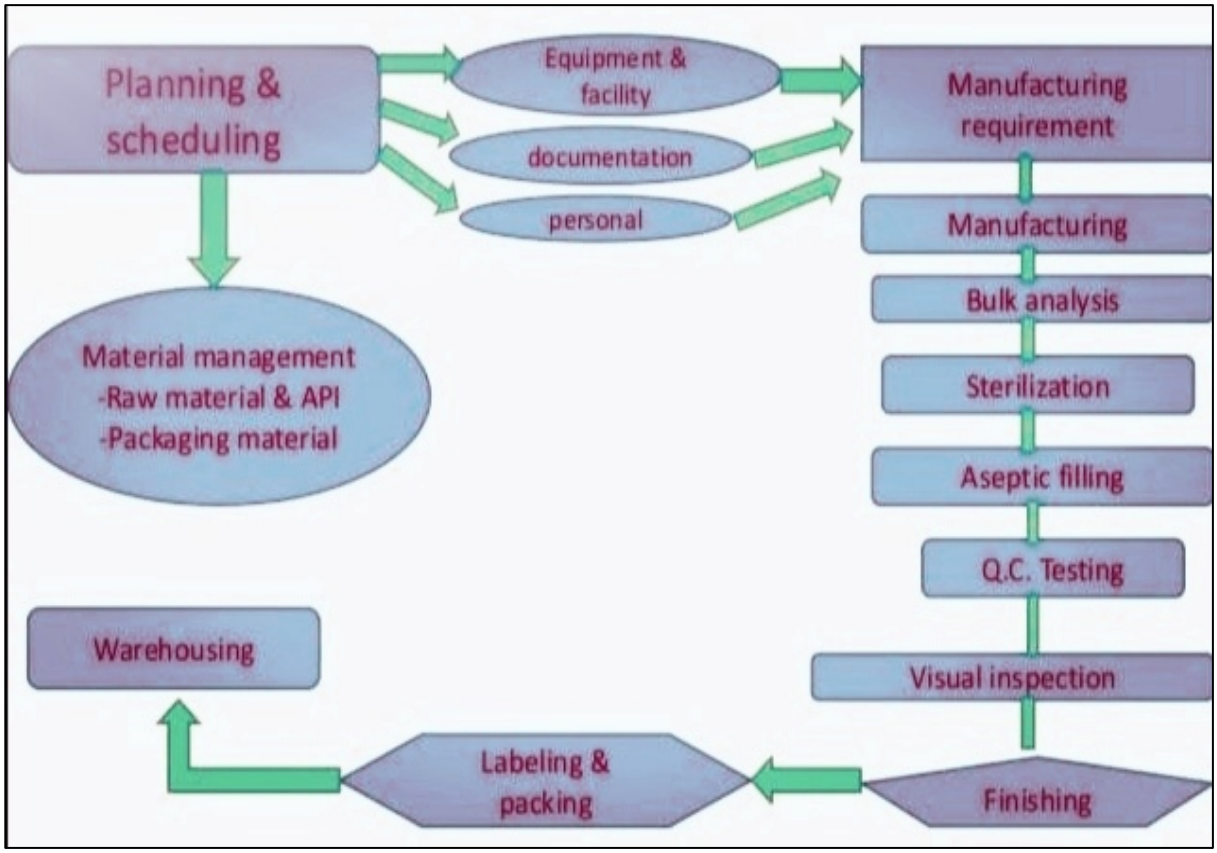



**Figure 05: Diagram represents finishing and packaging area in manufacturing of parenteral**

**METHODOLOGY**

**1. Filtration:** If the product is a solution, after its compounding, it should filter. Filtration process is employed for to clarify a solution and removing particulate matter down to 0.2µm in size will eliminate the micro-organisms. It is accomplished by cold sterilization.

Filters mainly functions by:

- Sieving or screening: The particles are retained on the surface of the filter by sieving
- Entrapment or impaction: If the particles smaller than the dimensions of the pore, they impact on the surface of the pore.
- Electrostatic attraction: Opposite charged particle to that of the surface of the filter pore to be adsorbed on the surface.

Membrane filters are used for parenteral preparations because they have high effective in particle- retention, non-shedding property, non-reactivity and have disposable characteristics also. The most common membranes are made up of cellulose esters, nylon, polycarbonate, PVDF, and Teflon. Membrane filters are disposable type and can be discarded after use. It should clean thoroughly while using. Most pharmaceutical industries that preparing parenterals uses 0.2 µm membrane filter (Thomas et al., 2018).

**2. Filling:** The solutions which sterilized through filtration are to be filled under the aseptic conditions. During the filling of product to the containers, should be for the prevention of contamination, especially the product is sterilized by the filtration and will not be sterilized in to the final container. The second one is called as aseptic fill and by using media fills it is validated. A liquid is more easily exposed uniformly into the container having the narrow mouth than is used for solid. Liquids which are mobile are easier to transfer and subdivide than viscous or sticky fluids, since these require heavy-duty machinery for the rapid production filling (Thomas et al., 2018).

**Liquid:** The filling of liquids into containers with high accuracy involves mainly three methods;

- Volumetric filling.
- Time/pressure filling.
- Net weight filling

Volumetric filling machines have pistons or peristaltic pumps. These are most common used method. Timepressure filling is used for filling of sterile liquids. A filling system is connected by a production tank that equipped with a pressure sensor. The sensor is used for the measurement of pressure and transmits values PLC system that controls the product flow from the tank to the filling manifold. The product is driven by using pressure mainly uses nitrogen with no pump mechanism. Time/pressure filling is preferable usually with the proteins that are sensitive to shear forces (Thomas et al., 2018).

**3. Sealing:** The filled containers should be filled as soon as possible to prevent the contents being contaminated. It represents the final aseptic procedure (Thomas et al., 2018).

**Ampoules:** Sealing of ampoules are done by melting of the portion of the glass neck. There are two types of sealing:-

- Pull - seals
- Tip - seals (bead - seals)

Tip seals are employed by melting the glass at the tip of the ampoule neck to form a bead like and close the opening. This is performed in a high temperature gas oxygen flame. Pull-seals are performed by heat the ampoule neck below the tip. The ampoule to be seal is rotated in the flame from a single burner. The tip is grasped and then pulled quickly from the ampoule body, when the glass is softens. Pull sealing process is slower one, but the sealing done by this is more secure than that of tip-sealing.

**Vials and Bottles:** By closing the opening using the rubber closure (stopper) the glass or the plastic vials are sealed properly. This should be done by after filling with care, to prevent the contamination of the contents inside. Increased chances for contamination are the large opening in the vials than the ampoules. The open containers must be protected from contamination, especially with the blanket of HEPA filtered laminar airflow. By using the aluminium caps the rubber stoppers are held in appropriate place. Rubber closures that uses for the intravenous administration have a permanent hole through the closure (Thomas et al., 2018).

**4. Sterilization:** Sterilization of parenteral products should be done after sealing it to the final container that is called as terminal sterilization. It should done within as short time

as that possible after the filling and sealing are fully completed. This is accomplished usually by the thermal process.

Radiation sterilization also will do to the parenteral finished products in sometimes. The care should be taken in the effect of the elevated temperature on the stability of the products. The elevated temperature that required for the sterilization by thermal process is adversely affects in many products like both pharmaceutical and biological. Non thermal methods are used for the heat-labile products. These non thermal methods include filtration through the bacteria retaining filters. Aseptic conditions should be strictly followed for all operations, and then only the contamination is not introduced into the filtrate. Dry-heat sterilization is performed for few dry solids that are not adversely affects by the high temperatures and that require long period of heating. For the sterilization of glassware and metal ware mostly performs the dry-heat sterilization process. After the sterilization process all the equipment will be sterile, dry and pyrogen-free.

Autoclaving (saturated steam under pressure) is the most common method used for sterilization process. It is the most effective sterilization method that used for the aqueous liquids or substances, since it can be reached or penetrated by the steam. Radiation sterilization is a terminal sterilization method with an ionizing radiation (gamma rays). There is an advantage for the applying on drugs in their final container, that also without any rise in temperature. One of the disadvantages is the possible formation of radiolytic products which leads to a change in the color and odor of the product (Maquille et al., 2006; Boyl, 2002).

**5. Packaging of Parenterals:** The USP includes certain requirements for the packaging and storage of injections:

i) The volume of injection in single-dose containers is defined as that which is specified for parenteral administration at one time and is limited to a volume of 1 Litre.

ii) Parenterals intended for intraspinal, intracisternal, or peridural administrations are packaged only in single-dose containers.

iii) Unless an individual monograph specifies otherwise, no multiple-dose container shall contain a volume of injection more than sufficient to permit the withdrawal and administration of 30 mL.

iv) Injections packaged for use as irrigation solutions or for hemofiltration or dialysis or for parenteral nutrition are exempt from the foregoing requirements relating to packaging. Containers for injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume in excess of 1 Litre.

v) Injections intended for veterinary use are exempt from the packaging and storage requirements concerning the limitation to single-dose containers and to volume of multiple-dose containers.

**Types of Containers:**

A. Glass containers

B. Plastic containers

## CONTAINERS & CLOSURES

**1. RUBBER CLOSURE:** Rubber closures are used to seal the openings of cartridges, Vials & bottles providing a material soft and elastic enough to permit entry and withdrawal of a hypodermic needle without loss of the integrity of the sealed container.

**Composition & Reactivity:** Rubber closures are formed of several ingredients:

- Natural rubber (latex) and/or a synthetic polymer.
- Vulcanizing agent usually sulfur.
- Accelerator one of the active organic compound 2-mercaptobenzothiazole.
- An activator usually Zinc oxide.
- Fillers such as carbon black or limestone.

**Table 05: Different ingredients used in rubber closures**

| Ingredients in Rubber Closures | Examples |
|---|---|
| **Elastomer** | Natural rubber (Latex), Butyl rubber, Neoprene |
| **Vulcanizing** | Sulfur, Peroxides |
| **Accelerator** | Zinc dibutyldithiocarbamate |
| **Activators** | Zinc oxide, Stearic acid |
| **Antioxidants** | Dilauryl thiodipropionate |
| **Plasticizers** | Paraffinic oil, Silicon oil |
| **Fillers** | Carbon black, Clay, Barium sulphate |
| **Pigments** | Inorganic oxides, Carbon black |

**Physical Properties:**

- Rubber closures must be sufficiently elastic to provide a snug fit between the closure & the neck and lip of the glass container.
- They must also spring back to close the hole made by the needle immediately after withdrawal.
- Rubber closures must not be so hard that they require an excessive pressure to insert the hypodermic needle, and in doing so must not produce a large number of fragments as the hollow needle cuts through the closure.
- Minimal water vapor transfer is important for example to prevent the absorption of water by freeze dried products. Plastic or lacquer coatings are sometimes applied to the surface that will be in contact with the product. These coatings sometimes reduce vapor transfer, sorption, & leaching but they do not usually provide the complete barrier desired.

**Chemical Properties:**

- Ideally closure should be completely non reactive with the product with which they are in contact.
- Two general compatibility problems exist, namely (A) Leaching of ingredients from rubber compound with subsequent reaction with ingredient of the product, & (B) Removal of ingredients from the product by sorption by the rubber compound or by vapor transfer through the closure.

**2. GLASS CONTAINERS:** Glass is still the preferred material for containers for injectable products. Glass is composed principally of Silicon dioxide tetrahedron, Modified physiochemical such as oxides as those of Sodium, Potassium, Calcium, Magnesium, Aluminium, Boron, & Iron.

The glass that is most resistant chemically is composed almost entirely of silicon dioxide, but it is relatively brittle and can only be melted at hightemperatures. Boric oxide modifies the characteristics as it enters the structural configuration but most of the other oxides enter the space within the structure & reduces the strength of the teratomic forces between the silicon & oxygen (Taurin et al., 2013).

**Table 06: Types of containers**

| Type of Containers | General Discriptions | Type of Tests | Tests Limits | | General Uses |
|---|---|---|---|---|---|
| | | | Size (ml) | ml of 0.02 N $H_2SO_4$ | |
| **I** | Highly resistance Borosilicate glass | Powdered glass | All | 1.0 | Buffered and Unbuffered aqueous solutions |
| **II** | Treated soda lime glass | Water attack | 100 or less<br>Over 100 | 0.7<br>0.2 | Buffered aqueous solutions with pH below 7.0<br>Dry powders oleaginous solutions |
| **III** | Soda lime glass | Powdered glass | All | 8.5 | Dry powders oleaginous solutions |
| **NP (Not Provided)** | General purpose Soda lime glass | Powdered glass | All | 15.0 | Not for parenterals For Tablets, Oral Suspensions, Ointments and External Liquids |

**Chemical Resistance:** The USP provides the Powdered glass & the Water attack tests for evaluating chemical resistance of glass. The test results are measures of the amount of alkaline constituents leached from the glass by purified water under controlled temperature conditions.

- The Powdered glass test is performed on ground, sized glass particles.
- The Water attack test is performed on whole container. The Water attack test is used only with containers that have been exposed to sulfur dioxide fumes under controlled humidity conditions. Such treatments neutralizes the surface alkaline oxides, thereby rendering the glass more resistant chemically.

**Physical Characteristics:**

- The protection of light sensitive products from the degradative effect of UV rays may be one of the most important physical characteristics of glass container. UV rays can be completely filtered out by the use of amber glass.
- The color of amber glass is largely produced by presence of iron oxide, traces of which may subsequently be leached into the product.
- If the product contains ingredient subjected to iron catalyzed chemical reaction, amber glass cannot be used. The product must then be protected from UV rays by mean of an opaque carton surrounding a colourless glass container.
- Glass container should have sufficient physical strength to withstand high pressure differential that develop during autoclaving and the abuse that occur during processing, shipping & storage.
- Low coefficient of thermal expansion to withstand the thermal shocks that occur during washing and sterilization procedures.
- Transparency to facilitate inspection of the containers.
- Uniform physical dimension to facilitate handling by the mechanical machinery used for automatic production operation.

Glass containers may be manufactured by drawing from glass tubing or by blow molding.

Ampuls, Cartridges & vials drawn from tubing have a thinner, more uniform wall thickness with less distortion than containers made by blow molding. Glass containers are sometimes coated internally with silicon fluid to produce a hydrophobic surface. To achieve permanency, the silicon must be baked at a temperature of approximately 1500 °C (3000 °F).

**Container Use Consideration:**

- The size of the single dose containers is limited to 1000 ml by the USP & multiple dose containers to 30 ml, unless permitted in a particular monograph.
- The size limitation for multiple dose vials is intended to limit the number of entries for withdrawing a portion of the content of the vials with theaccompanying risk of microbial contamination of the remaining contents.
- Single dose containers are intended to provide sufficient drug for just one dose, the integrity of container being destroyed when opened so that it cannot be reclosed and used again.
- Single dose container may range from liter bottles of intravenous solutions to 1ml, or smaller, cartridges.

**3. PLASTIC:** The principal ingredient of various plastic materials used for container is thermoplastic polymer. All of the polymeric materials except low density polyethylene & polystyrene can be autoclaved if they have been formulated with low amount of plasticizers.

**Physical Properties:**

- Plastic containers are used mainly because of light in weight, non breakable, low toxicity & low reactivity with products.
- Tissue toxicity can occur from certain polymers, but additives are a more common cause. Reactivity due to sorption has been found to occur most frequently with the polyamide, but additives leached from any of the plastic materials may interact with ingredient of product.
- Polyethylene and Polypropylene are the most commonly used polymer.

**Uses of Plastic:** Flexible polyethylene containers are used for ophthalmic solutions to be administered in drops, & Flexible polyvinyl chloride bags for intravenous solutions.

The USP has provided test procedures for evaluating toxicity of plastic materials. The test consist of 3 phases:

- Implanting small pieces of plastic material (IM route) in rabbits.
- Injecting eluates using Nacl injection, with & without alcohol, intravenously in mice & injecting eluates using PEG 400 & sesame oil intraperitoneally in mice.
- Injecting all 4 eluates subcutaneously in rabbits. The reaction from test samples must not be greater than non reactive control samples.

**EVALUATION OR QUALITY CONTROL TEST** (Saxena et al., 2012)

**1. LEAKER TEST:** Leaker test is employed to detect incompletely sealed ampoule so that they may be discarded. It is also used to test the package integrity. Package integrity reflects its ability to keep the product in and to keep potential contamination out.

**Causes of Leakage:**

- Leakage occurs when a discontinuity exists in the wall of a package that can allow the passage of gas under the action of a pressure or concentration differential existing across the wall.
- Presence of capillary pores can cause microbes to enter the ampoules or package may lead to the leakage of contents to outside. This may cause contamination of the sterile contents and also spoilage of appearance of the package.

**Table 07: Types of Leaker Tests**

| | |
|---|---|
| **A. Visual inspection**<br>• Visual inspection is the easiest leaker test method to perform.<br>• The method is used for the evaluation of large volume parenterals.<br>• To increase the sensitivity of the method the visual inspection of the sample container may be coupled with the application of vacuum to make leakage more readily observable.<br>**Advantage:** This method is simple & inexpensive.<br>**Disadvantage:** Less sensitive. | **B. Bubble test**<br>• The test package is submerged in liquids.<br>• A differential pressure is applied on the container.<br>• The container is observed for bubbles.<br>• Sometimes, surfactant added liquid is used for immersion of test package.<br>**Advantage:**<br>• The method is simple and inexpensive.<br>• The location of the leaks can be observed in this method. |
| **C. Dye test**<br>• The test container is immersed in a dye Jam.<br>• Vacuum and pressure is applied for sometime.<br>• The container is removed from the dye bath and washed.<br>• The container is then inspected for the presence of dye either visually or by means of UV spectroscopy.<br>• The dye used is usually 0.5% to 1% methylene blue. | **D. Vacuum ionization test**<br>• Vacuum ionization test is useful for testing leakage in the vials or bottled sealed under vacuum.<br>• This test is used for testing of the lyophilized products.<br>• High voltage, high frequency field is applied to vials which to cause residual gas, if present to glow.<br>• Glow intensity is the function of headspace vacuum level.<br>• The blue glow is the indicative of vacuum. |

**2. CLARITY TEST (PARTICLE CONTAINMENT TEST):** Clarity is a relative term, its mean a clear solution having a high polish conveys to the observer that the product is of exceptional quality and purity. Clarity test is carried out to check the particulate matter in the sample.

**Principle:** This test is performed to check the particulate contamination of injections and infusions consists of extraneous, mobile and undissolved particles, other than gas bubbles, unintentionally present in the solution.

**Table 08: USP limits for large volume infusions**

| **USP limits for large volume infusions** | |
|---|---|
| **Particle Size** | **Particle Limit** |
| 10 micrometre or larger / ml | 50 |
| 25 micrometre or larger / ml | 5 |

**Methods to detect particulate matter:** There are two methods can be used to detect particulate matter in parenteral products.

**Table 09: Methods to detect particulate matter**

| Test for Visible particles | Test for sub Visible particles |
|---|---|
| • In visual inspection, each injectable is inspected visually against white and black backgrounds.<br>• The white background helps in detection of dark coloured particles. The light or reflective particles will appear against the black background.<br>• Some visual enhancing aids can increase the efficiency. Magnifying lens at 2.5 x magnification set at the eye level facilitates the inspection.<br>• Visual inspection gives the **qualitative estimation** of the particulate matter. | This test is performed to check particulate contamination of injections and infusions consists of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.<br>**This is further divided into two methods:**<br>• **Method 1 (Light Obscuration Particle Count Test)** This method is preferable when examining injections and infusions for sub-visible particles<br>• **Method 2 (Microscopic Particle Count Test):** This method is used in case of preparations having reduced clarity or increased viscosity. Eg, Emulsions, colloids, and liposomal preparations |

## 3. TEST FOR PYROGENS / ENDOTOXINS

**PYROGEN:** In Greek "Pyro" means "fire" & "gen" means "beginning". A Pyrogen is a substance i.e. products of the growth of micro organisms or may be parts of dead cells or metabolic products which cause febrile reactions like fever, chills, back pain etc. The Pyrogen test is designed to limit the risk of febrile reaction following parentral administration of drugs.
It includes both In vitro and In vivo tests.

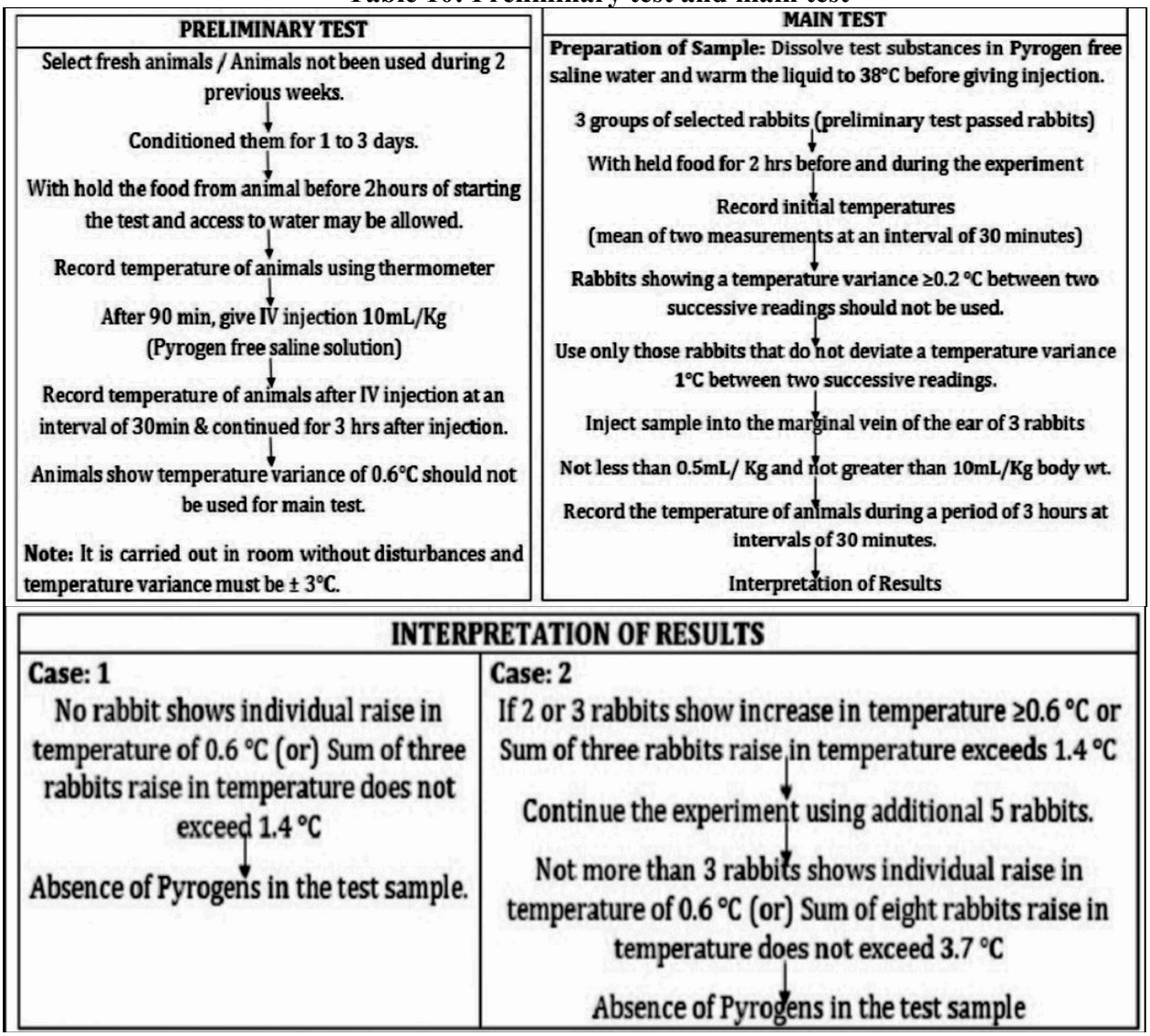
**A. In Vitro test (LAL Test - Limulus Amoebocyte Lysate Test):** In Vitro assay is used to detect the presence and concentration of bacterial endotoxins in drugs and biological products. Limulus Amoebocyte Lysate (LAL) is an aqueous extract of blood cells (amoebocytes) from the horseshoe crab, Limulus polyphemus. LAL reacts with bacterial endotoxin or lipopolysaccharide, which is a membrane component of Gram negative bacteria and forms gel which is then used for the detection and quantification of bacterial endotoxins.

**Limitations of LAL Test:**

- Disturbed by endotoxin binding components like lipids, blood components.
- Difficult to correlate with rabbit test.
- False positive for cellulose and many herbal preparations.

**B. In Vivo test (Rabbit Test: SHAM TEST)**:
**Principle:** The test involves the measurement of rise in body temperature of rabbits following IV injection of sterile solution of substance being examined.
**Animals Used:** Select same variety of healthy mature rabbits weighing less than 1.5Kg and should maintain balanced diet. They should not show any loss of body weight during the preceding week of test.
**Temperature Measurement:** Accurate temperature sensing devices such as Clinical Thermometer graduated in 0.1°C / Thermister / Probes are used to measure the temperature of rabbit. Insert the thermometer into the rectum of rabbit to a depth of not less than 6 cm and record the temperature.
**Materials Used:** Glass ware and syringes must be washed with water for injection and heated to 250°C for 30 minutes / 200°C for 1 hour in hot air oven.
**Procedure:** It includes: 1. Preliminary test & 2. Main test.

**Table 10: Preliminary test and main test**




| No. of Rabbits | Product passes if summed response does not exceed | Product fails if summed response exceeds |
|---|---|---|
| 3 | 1.15 °C | 2.65 °C |
| 6 | 2.80 °C | 4.30 °C |
| 9 | 4.45 °C | 5.95 °C |
| 12 | 6.60 °C | 6.60 °C |

**4. UNIFORMITY OF CONTENTS:** The test for uniformity of content of single-dose preparations is based on the assay of the individual contents of active substance(s) of a number of singledose units to determine whether the individual contents are within limits set with reference to the average content of the sample. The test is not required for multi-vitamin and trace-element preparations and in other justified and authorised circumstances.

**Method:** Using a suitable analytical method, determine the individual contents of active substances of 10 dosage units taken at random. Criteria for Tablets, Powders for parenteral administration, Ophthalmic inserts, Suspension for injection;

- The preparation complies with the test if each individual content is between 85% and 115 % of the average content.
- The preparation fails to comply with the test if more than one individual content is outside these limits.
- If one individual content is outside the limits of 85% to 115% but within the limits of 75% to 125%, determine the individual contents of another 20 dosage units taken at random.
- The preparation complies with the test if not more than one of the individual contents of the 30 units is outside 85% to 115% of the average content.

**5. STERILITY TEST:** There are two basic methods for sterility testing which are as follows:

**A. Direct Inoculation Method:**

- It involves the direct inoculation of product test samples into the culture media.
- It is suitable for samples with small volumes.
- Volume of the product is not more than 10 % of the volume of the medium.
- It is suitable for Aqueous solutions, Oily liquids, Ointments & Creams.

It involves three steps:

- Aseptically opening each sample container from a recently sterilized batch of product
- Using a sterile syringe and needle to withdraw the required volume of sample for both media from the container.
- Injecting one-half of the required volume sample into a test tube containing the required volume of Fluid Thioglycolate Medium and the other half volume of sample into a second test tube containing the required volume of TSB.

**Table 11: Volume requirements of direct transfer method**

| Container Content (ml) | Minimum Volume of Product (ml) | Minimum Volume of Medium (ml) |
|---|---|---|
| 10 or less | 1 | 15 |
| 10 - 50 | 5 | 40 |
| 50 - 100 | 10 | 80 |
| 100 - 500 | One half content | N/A |
| > 500 | 500 | N/A |
| Antibiotics (Liquids) | 1 | N/A |

**B. Membrane Filtration Method:** The technique of membrane filtration is used whenever the nature of the product permits, that is,

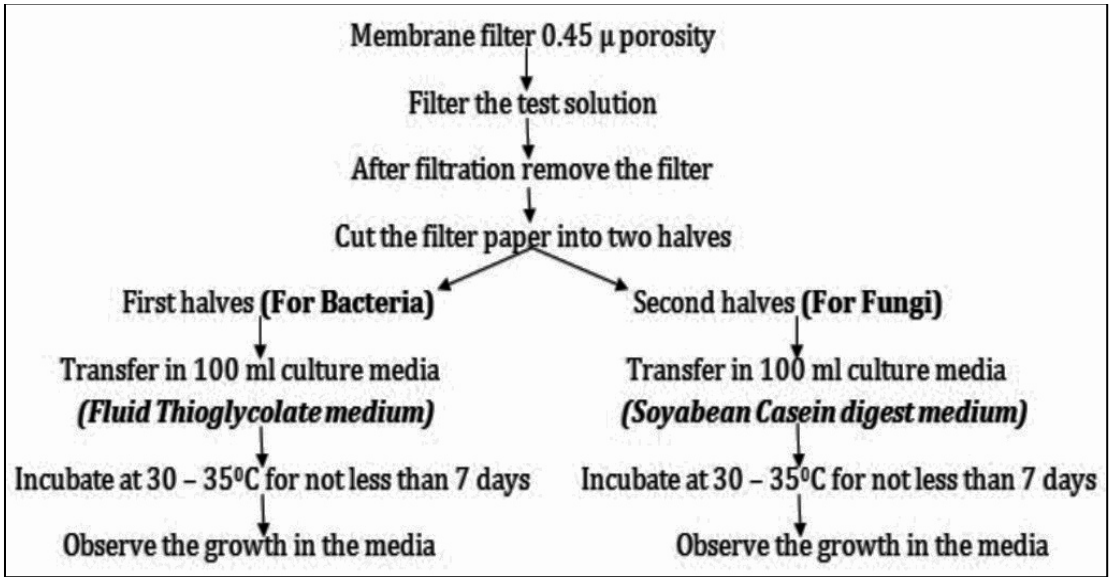
- For filterable aqueous preparation.
- For alcoholic or oily preparations.
- For preparations miscible with or soluble in aqueous or oily solvents provided these solvents do not have antimicrobial activity.

Use membrane filters having a nominal pore size of not greater than 0.45 µm with effectiveness to retain microorganisms.

**Table 12: Medium for membrane filtration test**

| MEDIUM FOR MEMBRANE FILTRATION TEST | |
|---|---|
| **FLUID THIOGLCOLLATE MEDIUM** | **SOYA BEAN CASEIN DIGEST MEDIUM** |
| • It is primarily intended for culture of anaerobic bacteria. It can also detect aerobic bacteria.<br>**Composition:**<br>• L. Cystine (0.5 g)<br>• Sodium chloride (0.75 g)<br>• Glucose monohydrate (5.5 g)<br>• Yeast extract (5 g)<br>• Pancreatic digest of casein (15 g)<br>• Sodium thioglycollate (0.5 g)<br>• Resazurin sodium soln. (1 ml)<br>• Water R (1000 ml)<br>• pH after sterilisation 7.1 + 0.2 | It is suitable for culture of both fungi and aerobic bacteria<br>**Composition:**<br>• Pancreatic digest of casein (17.0 g)<br>• Papaic digest of casein (3 g)<br>• Sodium chloride (5.0 g)<br>• Dipotassium hydrogen phosphate (2.5 g)<br>• Glucose monohydrate (2.5 g)<br>• Water R (1000 ml)<br>• pH after sterilisation 7.3 ± 0.2<br>• Prepare and sterilize the medium |

**Procedure:**




## PYROGENICITY

Water and packaging materials are the greatest sources of Pyrogens (pyrogenic contamination). Water used in parenteral and irrigating solutions should be free of Pyrogens. To achieve this proper control must be maintained in the preparation & storage of water.

Pyrogens are products of metabolism of microorganisms. Pyrogens, when present in parenteral drug products and injected into patients, can cause fever, chills, pain in the back and legs, and malaise.

The most potent pyrogenic substances (endotoxins) are constituents (lipopolysaccharides, LPS) of the cell wall of gram-negative bacteria (e.g., Pseudomonas sp, Salmonella sp, Escherichia coli).

Gram-positive bacteria and fungi also produce pyrogens but of lower potency and of different chemical nature. Gram positive bacteria produce peptidoglycans, whereas fungi product β-

glucans, both of which can cause nonendotoxin pyrogenic responses.
Endotoxins are lipopolysaccharides that exist in high molecular weight aggregate forms. However, the monomer unit of Lipopolysaccharide is less than 10,000 daltons, enabling endotoxin to easily pass through sterilizing 0.2 micron filters. The lipid portion of the molecule is responsible for the biological activity.
The intensity of the pyrogenic response and its degree of hazard are affected by:
Medical condition of the patient.
Potency of the Pyrogen.
Amount of the Pyrogen.
Route of administration (intrathecal is most hazardous followed by intravenous, intramuscular, and subcutaneous).

**Mechanism of Bacterial Pyrogens:** When bacterial (exogenous) pyrogens are introduced into the body, Lipopolysaccharide targets circulating mononuclear cells (monocytes and macrophages) that, in turn, produce pro-inflammatory cytokines, such as interleukin 2, interleukin 6, and tissue necrosis factor. Besides LPS, gram-negative bacteria also release many peptides (e.g., exotoxin A, peptidoglycan, and muramuyl peptides) that can mimic the activity of LPS and induce cytokine release.

**Detection of Pyrogens:** The Limulus Amebocyte Lysate (LAL) test can only detect the presence of LPS. It has been suggested that the Monocyte Activation Test, replace LAL as the official Pyrogen test, due to its greater sensitivity to all agents that induce the release of cytokines that cause fever.

**Sources of Pyrogens:** When micro-organisms metabolize, pyrogens will be produced. Therefore, raw water can be expected to be pyrogenic and only when it is appropriately treated to render it free from pyrogens, such as Water For Injection, should it be used for compounding the product or rinsing product contact surfaces, such as tubing, mixing vessels, and rubber closures. Even when such rinsed equipment and supplies are left wet and improperly exposed to the environment, there is a high risk they will become pyrogenic.
Solutes may be a source of pyrogens. For example, the manufacturing of bulk chemicals may involve the use of pyrogenic water for process steps, such as crystallization, precipitation, or washing. Bulk drug substances derived from cell culture fermentation will almost certainly be heavily pyrogenic. Therefore, all lots of solutes used to prepare parenteral products should be tested to ensure they will not contribute unacceptable quantities of endotoxin to the finished product.

**Control of Pyrogens**: Pyrogens may enter a preparation through any means that will introduce living or dead micro-organisms. However, current technology permits the control of such contamination, and the presence of pyrogens in a finished product indicates processing under inadequately controlled conditions.
Pyrogens can be destroyed by heating at high temperatures. A typical procedure for depyrogenation of glassware and equipment is maintaining a dry heat temperature of 250°C for 45 min. Exposure of 650°C for 1 min or 180°C for 4 hours, likewise, will destroy pyrogens. The usual autoclaving cycle will not do so.
Heating with strong alkali or oxidizing solutions destroys pyrogens.

## WATER FOR INJECTION

Water for injection (WFI) usually is prepared by distillation in a still specifically designed to produce high quality water required.
The specification for still should include:
i) Prepurification of feed water by Chemical softening, Deionization, or Filtration to improve the quality of the distillate and reduce the frequency of requiredcleaning due to insoluble scale in boiler.
ii) Removal of entrained contaminants from the vapor before it is condensed by passage through an efficient baffle system
iii) Ejection of volatile constituents from the top of the system before the vapor is cooled so that

they will not redissolve and appear in the condensate.

iv) Construction of all surface that will come in contact with the vapor and condensate of a material that will not dissolve in even trace amounts, preferably pure tin, 304 stainless steel or borosilicate glass (Noh et al., 2013).

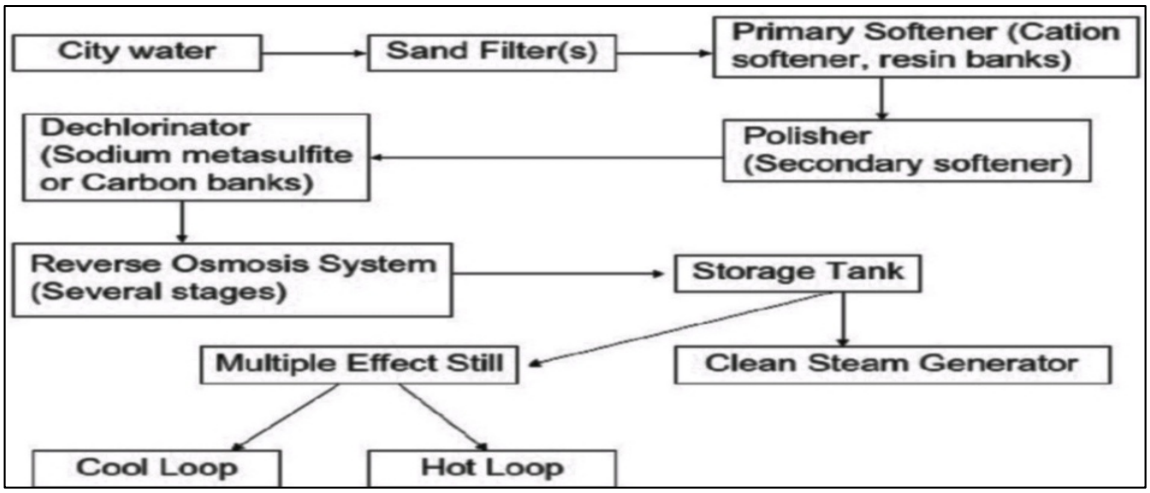



**Figure 06: A schematic of a typical process used to convert portable water to water for injection**

In addition to conventional still, two types of stills frequently used for the production of large volumes of water are the Vapor compression stills & Multiple effect stills.

**A. Compression Distillation:** The vapor-compression still, primarily designed for the production of large volumes of high-purity distillate with low consumption of energy and water.

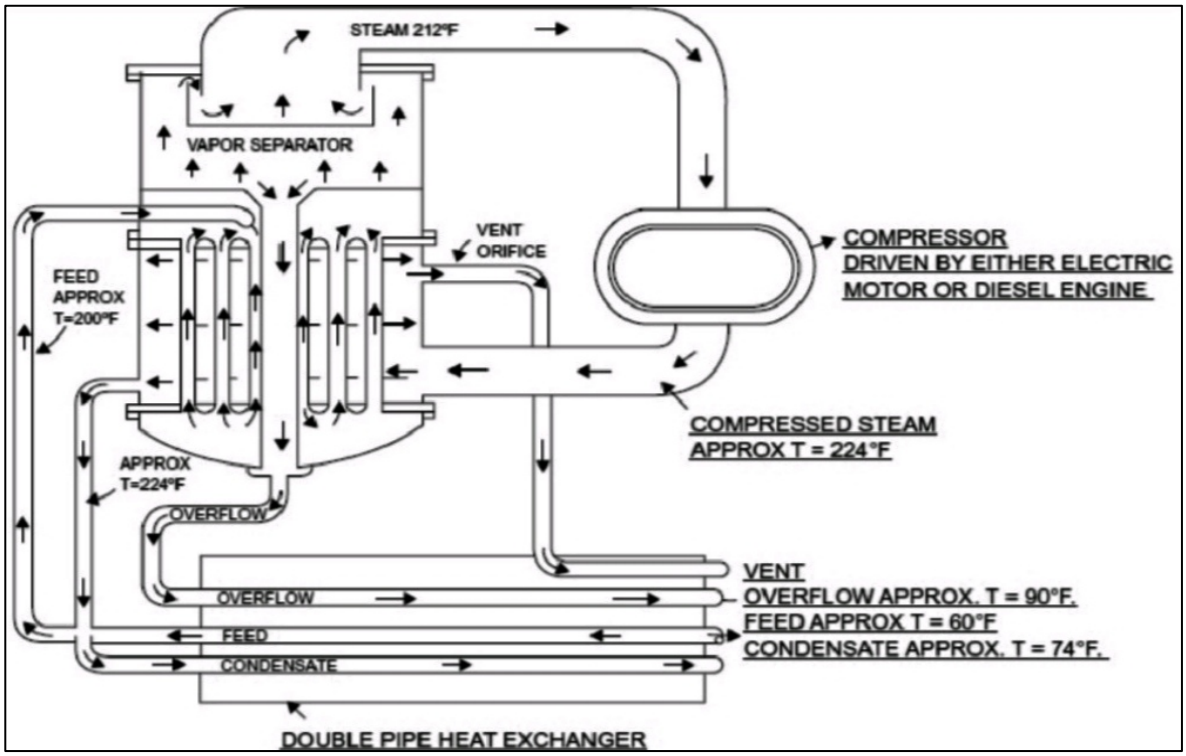



**Figure 07: Vapor Compressor Still**

To start, the feed water is heated from an external source in the evaporator to boiling. The vapor produced in the tubes is separated from the entrained distilland in the separator and conveyed to a compressor that compresses the vapor and raises its temperature to approximately 107°C. It then flows to the steam chest, where it condenses on the outer surfaces of the tubes containing the distilland; the vapor is, thus, condensed and drawn off as a distillate, while giving up its heat to bring the distilland in the tubes to the boiling point. Vaporcompression stills are available in capacities from 50 to 2800 gal/hr.

**B. Multiple-Effect Stills:** The multiple-effect still is also designed to conserve energy and water usage. In principle, it is simply a series of single-effect stills or columns running at differing pressures where phase changes of water take place. A series of up to seven effects may be used, with the first effect operated at the highest pressure and the last effect at atmospheric pressure.

Steam from an external source is used in the first effect to generate steam under pressure from feed water; it is used as the power source to drive the second effect. The steam used to drive the second effect condenses as it gives up its heat of vaporization and forms a distillate. This process continues until the last effect, when the steam is at atmospheric pressure and must be condensed in a heat exchanger.

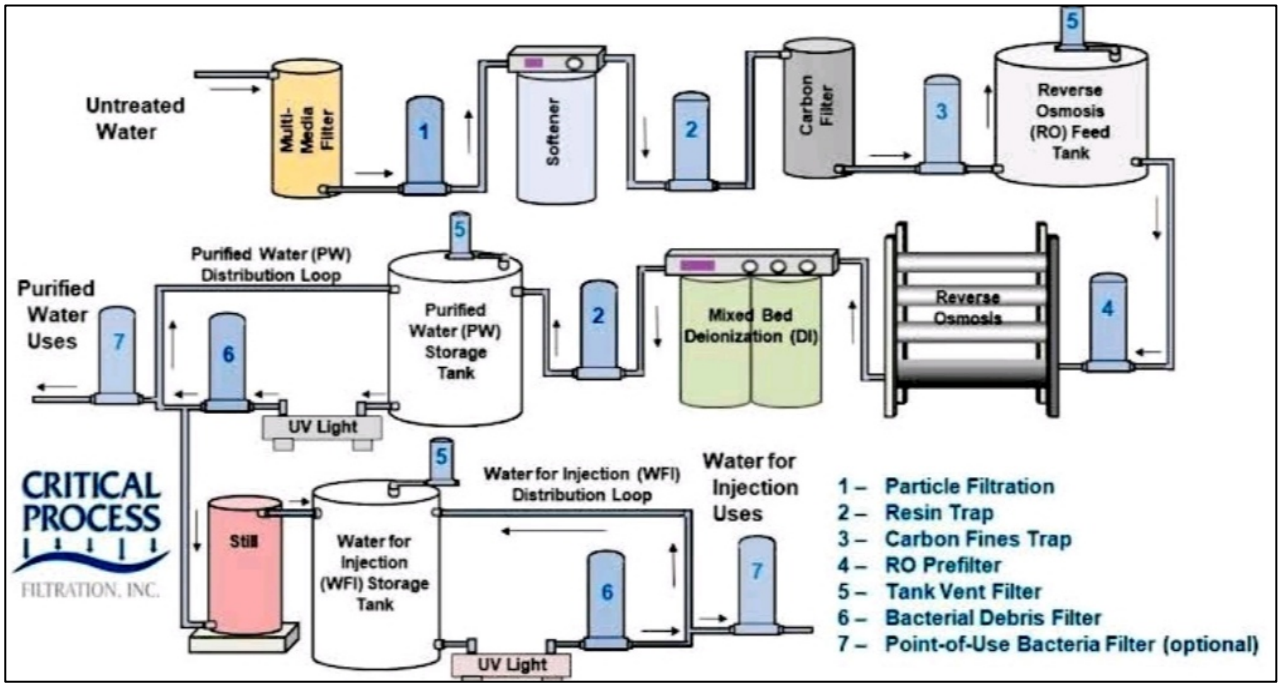



**Figure 08: Multiple effect water for injection distillation**

The capacity of a multiple-effect still can be increased by adding effects. The quantity of the distillate will also be affected by the inlet steam pressure; thus, a 600-gal/hr unit designed to operate at 115 psig steam pressure could be run at approximately 55 psig and would deliver about 400 gal/hr. These stills have no moving parts and operate quietly. They are available in capacities from about 50 to 7000 gal/hr.

**Types of Water for Injection**

**1. Water for injection USP**

- It is water obtained by distillation or reverse osmosis.
- It conforms to the standards of purified water. It cannot contain more than 10 ppm of total solid & should have a pH between 5 & 7.

- It is free of Pyrogens & can be used as solvent for preparation of parenteral solutions.

**2. Sterile water for injection USP**

- It is water for injection that is sterilized & packaged in single dose container of Type 1 & 2 glass.
- These containers do not exceed a capacity of 1 liter.

**3. Bacteriostatic water for injection USP**

- It is sterile water for injection that contains one or more suitable antimicrobial agents.
- It is packaged in single dose or multiple dose container of Type 1 & 2 glass.
- These containers do not exceed the capacity of 30 ml.

**4. Sterile water for irrigation USP**

- It is water for injection that is sterilized & packaged which do not contains any antimicrobial agents or other added substances.

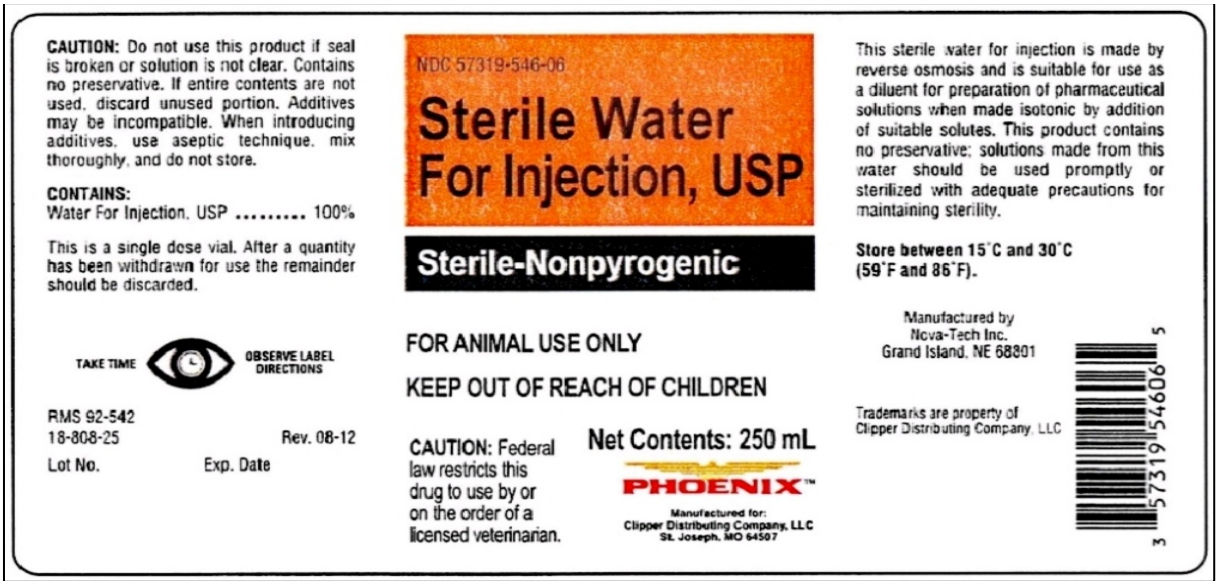



**Figure 09: Represents labell for steril water for injection USP**

## LABELLING

The term "label" designates that part of the labeling upon the immediate container. The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container or upon, or in, any package or wrapper in which it is enclosed, with the exception of the outer shipping container.

The labeling of an injection must provide the physician or other user with all information needed to ensure the safe and proper use of the product.

The label should states:

- The name of the preparation.
- The percentage content of drug of a liquid preparation.
- The amount of active ingredient of a dry preparation.
- The volume of liquid to be added to prepare an injection or suspension from a dry preparation.
- The route of administration.
- Statement of storage conditions.
- Expiration date.

The label must state the name of the vehicle and the proportions of each constituent, if it is a mixture, and the names and proportions of all substances added to increase stability or usefulness.

Also, the label must indicate the name of the manufacturer or distributor and carry an identifying lot number. The lot number is capable of providing access to the complete manufacturing history of the specific package, including each single manufacturing step.

The container label is so arranged that a sufficient area of the container remains

uncovered for its full length or circumference to permit inspection of the contents.

Preparations labeled for use as dialysis, hemofiltration, or irrigation solutions must meet the requirements for injections, other than those relating to volume, and must also bear on the label statements that they are not intended for intravenous injection.

Injections intended for veterinary use are so labeled.


**Figure 10: Labels of some parenterals products**

**Controlled Environment Required for Parenteral Preparation:**

**Clean Room Classified Areas:** Due to the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments (clean rooms) in which these products are manufactured (Tan et al., 2013).

The Critical and General area of clean room: The clean room divides into two areas.

1. Critical Area
2. General Area

The critical area is the area around the point of the production where contamination can gain direct access to the process. This area often protected by localized laminar flow clean benches and workstations. The General area is the rest of the clean room where contamination will not gain direct entry into the product but should be kept clean because of the transfer of contamination into the critical area. It is necessary that the critical area be cleaned most often with the best cleaning ability without introducing contamination ( Ma et al., 2012; Liu et al., 2014; Zheng et al., 2013).

**Classification of Clean Rooms**: The class is directly related to the number of particles per cubic foot of air equal to or greater than 0.5 micron.

**1. Class 100,000:** Particle count not to exceed a total of 100,000 particles per cubic foot of a size 0.5µ and larger or 700 particles per foot of size 5.0µ and larger.

**2. Class 10,000:** Particle count not to exceed a total or 10,000 particles per cubic foot of a size 0.5µ and larger or 65-70 particles per cubic foot of a size 5.0µ and larger.

**3. Class 1,000:** Particles count not to exceed a total of 1000 particles per cubic foot of a size 0.5µ and larger or 10 particles per cubic foot of a size 5.0µ and larger.

**4. Class 100:** Particles count not to exceed a total of 100 particles per cubic foot of a size 0.5µ and

larger (Ashjari et al., 2012; Jin et al., 2012; Feng et al., 2012).
**Class 1:** The particle count shall not exceed a total of 3000 particles/m3 of a size 0.5µ.
**Class 2:** The particle count shall not exceed a total of 3000 particles/m3 of a size of 0.5µ or greater; 2000 particles/m3 of size 0.5µ or greater; 30 particles of a size 10µ.
**Class 3:** The particle count shall not exceed a total of 1,000,000 particles of a size of 1µ or greater; 20,000 particles/m3 of size 5µ or greater; 4000 particles/m3 of a size 10µ or greater; 300 particles of a size of 25µ or greater.
**Class 4:** The particle count shall not exceed a total of 200,000 particles of a size of 5µ or greater. For the manufacture of sterile medicinal products normally 4 grades can be distinguished:
**GRADE - A:** The local zone for high risk operations. eg. filling zone, stopper bowls, open ampules and vials.
**GRADE - B:** In case of aseptic preparation and filling, the back ground environment for grade - A zone.
**GRADE - C & D:** Clean areas for carrying out less critical stages in the manufacture of sterile produce (Liu et al., 2014; Zheng et al., 2013; Vadakkan et al., 2013).

## DISCUSSION AND CONCLUSION

This report presents a summary of pharmaceutical development of an injectable solution. It emphasizes a science and risk based approach to product and process development and presents findings as a knowledgebased report, where relevant, supporting data havebeen summarized in appropriate dosage form or illustrations. Formulation development involved the use of prior knowledge and structured experimentation to investigate the relationship between formulation component levels, API attributes and the drug product quality attributes. Using prior knowledge the material attributes and process parameters, which could have an impact upon final product quality, were identified. The liquid injection tested for its sterility, Bacterial endotoxin test. The tests passes by obtaining a sterile solution and the bacterial endotoxin test obtained within the specification limits. . Particulate matter count assessed by using light obscuration method and the test passes for the solution by obtaining free from the foreign particles.

The most effective route for the delivery of the active pharmaceutical substances is the parenteral rout of administration, prescribed to unconscious patients .It was concluded that parenteral route of administration is the most effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious patients.

The review deals with data related to parenteral as as liquid dosage form including its classification and types of parenteral products, route of administration, preformulation factors, formulation of parenterals, manufacturing of parenterals, evaluation of parenteral products, pyrogenicity, water for injection was successfully studied. It is more significant to produce good quality of parenteral. Parenterals are the pyrogen free liquids these are manufactured and stored according to GMP guidelines. Proper area environmental control, personnel observation will gives excellent parenteral products and attain their described therapeutic effect.

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