

Community Pharmacy

Sterile Formulations

- Sterile formulations are pharmaceutical preparations that are free from viable microorganisms (bacteria, fungi, etc.) and foreign particles, designed for administration via injection, infusion, or instillation into the body.
- These preparations bypass natural defense barriers (e.g., the gastrointestinal tract), making sterility, isotonicity, and compatibility absolutely critical.

Parenterals are classified into:

- **Small Volume Parenterals (SVPs)** – ≤ 100 mL
- **Large Volume Parenterals (LVPs)** – > 100 mL (usually 250–1000 mL or more)

Importance of Sterility in Parenterals

- They are administered directly into the bloodstream, tissues, or body cavities, hence any contamination may lead to:
 - Sepsis
 - Pyrogenic (fever-causing) reactions
 - Toxicity
 - Patient death in severe cases
- Therefore, **absolute sterility**, **absence of pyrogens (endotoxins)**, and **particulate control** are mandatory.

Components of Sterile Parenteral Formulations

1. **Active Pharmaceutical Ingredient (API):** Drug substance.
2. **Vehicle:** Usually sterile Water for Injection (WFI), sometimes oils (for IM use).
3. **Excipients:**
 - **Buffers** (e.g., phosphate, citrate): to maintain pH.
 - **Tonicity Adjusters** (e.g., NaCl, dextrose): to make solution isotonic with body fluids.
 - **Solubilizers** (e.g., PEG, propylene glycol): for poorly soluble drugs.
 - **Preservatives** (e.g., benzyl alcohol): used in **multi-dose** vials only.
4. **Container and Closure System:**
 - Glass vials, ampoules, IV bags, prefilled syringes.
 - Rubber stoppers (for vials) must not react with the drug.
5. **Labeling and Protective Packaging** to ensure product integrity during transport.

Large Volume Parenterals (LVPS)

Definition:

- Large Volume Parenterals are sterile solutions intended for intravenous infusion, typically supplied in volumes of **100 mL or more** (common volumes: 250 mL, 500 mL, 1000 mL).
- They do not contain any bacteriostatic agent due to their high volume and continuous infusion use.

Common Examples:

- Dextrose Injection 5% w/v
- Sodium Chloride Injection 0.9% w/v (Normal Saline)
- Ringer's Lactate Solution
- Total Parenteral Nutrition (TPN) Solutions

Formulation Requirements:

- Must be **sterile**, **pyrogen-free**, and **isotonic**
- pH must be within physiological range (usually 4–9)
- Must be free of visible particulates
- Should not contain bacteriostatic agents (especially for neonates)

Formulation Methods (Detailed):

1. Selection of Ingredients:

- **Active pharmaceutical ingredient (API):** must be stable in aqueous solution.
- **Solvents:** mostly Water for Injection (WFI).
- **Electrolytes and Osmotic Agents:** added to maintain isotonicity.
- **Buffers:** to maintain pH (e.g., phosphate or acetate buffers).
- **Stabilizers/Antioxidants:** e.g., sodium metabisulfite, EDTA.

2. Solution Preparation:

- All ingredients are weighed and dissolved in WFI.
- Solution is filtered using 0.22-micron filters to remove particles.

3. Filling and Sealing:

- The solution is filled into glass or plastic containers (commonly via aseptic filling).
- Sealing is done using rubber closures and aluminum caps or fusion-sealing (for plastic).

4. Sterilization:

- Terminal sterilization by autoclaving at 121°C for 15–20 minutes (preferred method).

- Heat-sensitive solutions are filled under aseptic conditions and sterilized by filtration.

5. Inspection:

- Containers are visually inspected for particulates, cracks, and volume.

Evaluation Techniques for LVPs:

1. Sterility Testing:

- Must comply with pharmacopeial guidelines (e.g., USP <71>).
- Incubation in fluid thioglycollate and soybean casein digest medium for 14 days.

2. Pyrogen Testing:

- Performed using the Rabbit Test or LAL (Limulus Amebocyte Lysate) Test for endotoxins.

3. Particulate Matter Testing:

- Using light obscuration or microscopic particle count test.

4. pH Testing:

- Measured with a calibrated pH meter.

5. Osmolality Test:

- Ensures isotonicity; conducted with an osmomètre.

6. Assay and Content Uniformity:

- Ensures correct amount of API is present.

7. Visual Inspection:

- Manual or automated for clarity, foreign particles, and defects.

Advantages of LVPs:

- Useful for fluid and electrolyte replacement.
- Allows for high-volume administration of nutrients and medications.
- Ensures immediate therapeutic action via IV route.
- Provides complete bioavailability.
- Suitable for continuous infusion over hours/days.

Disadvantages of LVPs:

- Requires trained personnel for administration.
- Strict aseptic conditions must be maintained.
- Cannot be self-administered.
- Risk of pyrogenicity, air embolism, or infection if improperly handled.
- Limited shelf-life once opened.

- Potential for precipitation or instability with some drugs in large volume.

Small Volume Parenterals (SVPS)

Definition:

- Small Volume Parenterals (SVPs) are sterile, pyrogen-free injectable solutions or suspensions with a volume of less than 100 mL, typically ranging from 1 mL to 100 mL.
- They are used for intravenous (IV), intramuscular (IM), subcutaneous (SC), intradermal (ID), or other specialized routes such as intrathecal or intra-articular administration.

Common Volumes:

- 1 mL, 2 mL, 5 mL, 10 mL, 20 mL, 50 mL

Examples:

- Adrenaline Injection (1 mL)
- Ceftriaxone Injection (IV/IM)
- Insulin Injection
- Heparin Injection
- Multivitamin Injections
- Vaccines

Formulation Requirements:

- Must be sterile and pyrogen-free
- Must be free of visible particulate matter
- Must be isotonic (for IV use) to prevent pain or hemolysis
- pH must be compatible with body tissues (ideally between 4–9)
- May contain preservatives (e.g., benzyl alcohol, phenol) for multi-dose vials
- Stabilizers, antioxidants, buffers may be used based on API requirements

Formulation Methods (Detailed):

1. Pre-formulation Studies:

- **Solubility:** Ensuring drug is soluble or appropriately suspended in WFI or co-solvents
- **Stability:** Analyzing degradation in presence of water, heat, oxygen, light
- **Compatibility:** With container materials and excipients

2. Selection of Ingredients:

- **Active Drug:** Based on therapeutic dose

- **Solvent:** Primarily Water for Injection (WFI); co-solvents like ethanol, PEG may be used
- **Tonicity Adjusters:** Sodium chloride, dextrose
- **Buffers:** Phosphate, citrate, acetate (to maintain pH)
- **Preservatives:** For multidose vials, e.g., methylparaben, benzyl alcohol
- **Stabilizers/Antioxidants:** Sodium metabisulfite, EDTA

3. Solution/Suspension Preparation:

- Dissolution of solutes in WFI in a stainless steel mixing vessel under aseptic conditions
- For suspensions, the API is micronized to reduce particle size and prevent sedimentation
- Homogenization and filtration to achieve a clear, particulate-free solution

4. Sterile Filtration:

- Through 0.22-micron membrane filters into sterile, depyrogenated containers

5. Filling and Sealing:

- Done under Class 100 aseptic conditions in cleanrooms
- Filled into ampoules, vials, or pre-filled syringes using automated or semi-automated machines
- **Sealing:**
 - Ampoules are flame-sealed
 - Vials are stoppered and sealed with aluminum caps
 - Pre-filled syringes are capped and crimped

6. Sterilization:

- **Heat stable products:** Terminal sterilization in autoclaves (121°C for 15-20 mins)
- **Heat-sensitive products:** Sterile filtration and aseptic processing

7. Labeling and Packaging:

- Labeled with product name, strength, route, storage, batch number, etc.
- Packed in boxes with inserts (where required)

Evaluation Techniques:

1. Sterility Testing:

- Carried out as per pharmacopeial standards (e.g., USP <71>)
- Incubation in thioglycollate and soya-bean casein digest media for 14 days

2. Pyrogen Testing:

- **Rabbit Test** or **LAL Test** (preferred, more sensitive)



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