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INDUSTRIAL PHARMACY - I

UNIT 4

TOPIC :

- **Parenteral Products :**

  a. Definition, types, advantages and limitations. Preformulation factors and essential requirements, vehicles, additives, importance of isotonicity

  b. Production procedure, production facilities and controls, aseptic processing

  c. Formulation of injections, sterile powders, large volume parenterals and lyophilized products.

  d. Containers and closures selection, filling and sealing of ampoules, vials and infusion fluids. Quality control tests of parenteral products.

Parenteral Products

- Parenteral products are sterile preparations intended for administration by injection, infusion, or implantation into the body through the skin or mucous membranes using a syringe, needle, or infusion set.
- They bypass the alimentary canal and directly enter systemic circulation or specific tissues.

Examples :

- Injections
- Infusions
- Implants
- Irrigations
- Ophthalmic injections

Types of Parenteral Products

Type	Description	Example
1. Small Volume Parenterals (SVPs)	Volume ≤ 100 mL; used for single-dose or multi-dose injections.	Insulin injection, Adrenaline injection
2. Large Volume Parenterals (LVPs)	Volume > 100 mL; used for fluid replacement or nutrient supply.	Dextrose Injection, Normal saline
3. Single-Dose Injections	Used once and discarded; contain no preservatives.	Vaccines, Morphine injection
4. Multi-Dose Injections	Contain preservatives for repeated use.	Insulin, Heparin injection
5. Dry Powder for Injection	Reconstituted with sterile water before use.	Ceftriaxone, Ampicillin
6. Implants	Solid or semisolid dosage forms inserted under skin for prolonged release.	Hormone implants, Contraceptive rods
7. Suspensions/Emulsions for Injection	Insoluble or lipid-based drug formulations for	Depot injections, Propofol emulsion

	sustained release.	

Advantages of Parenteral Products

1. Rapid onset of action — ideal for emergencies.
2. 100% bioavailability (no first-pass metabolism).
3. Suitable for unconscious or uncooperative patients.
4. Useful for drugs inactivated in the GIT (e.g., insulin, penicillin).
5. Accurate and predictable dose delivery.
6. Controlled release possible via depot formulations or implants.
7. Immediate therapeutic response in life-threatening conditions.

Limitations of Parenteral Products

1. Painful administration due to needles.
2. Requires skilled personnel for injection.
3. Sterility must be maintained, increasing production cost.
4. Risk of infection and tissue injury if not properly administered.
5. Difficult to remove once administered (no recall).
6. Expensive manufacturing, packaging, and handling.
7. Short shelf life compared to oral formulations.

Preformulation Factors and Essential Requirements

- Before developing a parenteral formulation, certain preformulation studies are essential to ensure stability, compatibility, and safety.

A. Preformulation Factors

1. Physicochemical properties of drug
    - Solubility, pH, partition coefficient, and stability in water and solvents.
    - Determines the choice of vehicle and need for additives.
2. Compatibility with excipients
    - Must not react with vehicle, stabilizers, or containers.
3. Sterility and pyrogenicity
    - Product must be free from microorganisms and pyrogens (fever-producing substances).
4. pH and buffering
    - Must be within physiological limits (≈ 7.4) for patient comfort and stability.
5. Tonicity
    - Should be isotonic with blood to prevent pain or hemolysis.
6. Particle size
    - Small and uniform to avoid embolism and ensure smooth injection.
7. Viscosity
    - Should allow easy injection through a syringe.

B. Essential Requirements for Parenteral Products

1. Sterility:
    - Must be completely free from living microorganisms.
    - Achieved by sterilization methods (autoclaving, filtration, etc.).
2. Freedom from Pyrogens:
    - Pyrogens cause fever when injected.
    - Removed by depyrogenation (dry heat at 250°C).

3. Isotonicity:
    - Parenterals should have osmotic pressure equal to blood plasma (~0.9% NaCl).
4. Clarity and Freedom from Particulate Matter:
    - Solutions must be clear and free from visible particles.
5. Stability:
    - Chemical, physical, and biological stability must be ensured during shelf life.
6. Compatibility:
    - Container and closure must not react or adsorb the drug.
7. Aseptic Preparation:
    - Prepared under aseptic conditions in clean rooms (Class 100).
8. Proper Labeling and Packaging:
    - Include route, dose, storage, and preservative information.

Vehicles for Parenteral Products

Vehicles act as solvents or carriers for the drug. They must be non-toxic, non-irritating, stable, and compatible.

A. Aqueous Vehicles

1. Water for Injection (WFI):
    - Most commonly used vehicle.
    - Sterile, pyrogen-free, and freshly prepared.
2. Sterile Water for Injection:
    - Packaged in single-dose containers (not isotonic).
3. Bacteriostatic Water for Injection:
    - Contains antimicrobial agents (e.g., benzyl alcohol) for multi-dose use.
4. Sodium Chloride Injection (0.9% NaCl):
    - Used when isotonicity is required.
5. Ringer's and Lactated Ringer's Solution:
    - Used for electrolyte and fluid replenishment.

B. Non-Aqueous Vehicles

Additives Used in Parenteral Formulations

- Additives are non-therapeutic agents that are intentionally included in a formulation to improve stability, solubility, tonicity, or performance of the active ingredient without interfering with its therapeutic efficacy or causing toxicity.

Functions of Additives

Additives are used to:

- Adjust pH and tonicity
- Enhance solubility of the drug
- Improve stability (against oxidation, hydrolysis, light, etc.)
- Prevent microbial growth
- Ensure uniform dispersion or suspension
- Facilitate isotonicity adjustment
- Aid in product preservation and compatibility

Common Types of Additives

A. Antimicrobial Agents (Preservatives)

- Purpose: Prevent microbial growth in multiple-dose containers during use.
- Requirements: Must be non-toxic, effective at low concentrations, and compatible with the drug and vehicle.

Examples:

Type	Examples	Concentration Range	Remarks
Phenolic compounds	Phenol, Cresol	0.25–0.5%	Broad antimicrobial activity
Alcohols	Benzyl alcohol	1–2%	Also acts as a local anesthetic
Quaternary ammonium compounds	Benzalkonium chloride	0.01%	Effective against Gram-positive bacteria
Organic mercurials	Thiomersal	0.001–0.01%	Used rarely due to toxicity

Note: Preservatives are *not used* in single-dose injections, spinal, or intrathecal preparations.

B. Buffers

- Purpose: Maintain pH within a stable and physiologically acceptable range to ensure drug stability and comfort upon injection.
- Common pH range: 3.0–9.0 depending on drug and route.
- Requirements: Should have minimal toxicity and buffering capacity to allow pH adjustment by body fluids after injection.

Examples:

- Acetate buffer
- Citrate buffer
- Phosphate buffer

C. Antioxidants

- Purpose: Prevent oxidative degradation of drugs susceptible to oxidation (e.g., vitamins, adrenaline, fats, and oils).
- Mechanism: They act by scavenging oxygen or free radicals or forming complexes with trace metals that catalyze oxidation.

Examples:

Aqueous systems	Non-aqueous systems	Synergists
Sodium metabisulfite	Butylated hydroxytoluene (BHT)	Citric acid
Sodium bisulfite	Butylated hydroxyanisole (BHA)	Tocopherols
Ascorbic acid	Propyl gallate	Lecithin

Note: Sulfites should be avoided in sensitive patients (e.g., asthmatics).

D. Chelating Agents (Sequestering Agents)

- Purpose: Prevent oxidation by forming complexes with heavy metal ions that catalyze oxidation.
- Examples:
  - Disodium edetate (EDTA)
  - Citric acid

Often used in combination with antioxidants for synergistic protection.

E. Solubilizing Agents (Co-solvents and Surfactants)

- Purpose: Enhance solubility of poorly water-soluble drugs.
- Requirements: Must be non-toxic, non-irritant, and compatible with parenteral use.

Examples:

- Co-solvents: Ethanol, Propylene glycol, Polyethylene glycol (PEG 400), Glycerin.
- Surfactants: Polysorbates (Tween 20, Tween 80), Cremophor EL, Sodium lauryl sulfate (rarely).

Importance of Isotonicity

- Isotonicity refers to the condition where the osmotic pressure of a solution equals that of body fluids (blood plasma, tears).

Importance:

1. Prevents pain or irritation at the injection site.
2. Avoids hemolysis or crenation of red blood cells.
3. Maintains tissue integrity and comfort.
4. Ensures safety and stability of parenteral formulations.

Common Isotonic Solutions:

- 0.9% Sodium Chloride solution
- 5% Dextrose solution

Methods of Adjustment:

- Cryoscopic method
- Sodium chloride equivalent method
- Freezing point depression method

Production Procedure of Parenteral Products

- The manufacturing of parenteral products is a highly specialized process requiring strict aseptic conditions, trained personnel, and sterile facilities. The overall aim is to produce sterile, pyrogen-free, particulate-free products.

A. Steps in Production of Parenteral Products

Stage	Purpose	Description
1. Raw Material Preparation	Ensure quality of ingredients	All raw materials (API, excipients, solvents, containers) are tested for purity, sterility, and compatibility. Only high-grade materials are used.
2. Solution or Suspension Preparation	Formulate the drug	The drug and excipients are dissolved or dispersed in a suitable vehicle (aqueous or non-aqueous) under aseptic or controlled conditions. Mixing tanks with stirrers are used.
3. Filtration	Remove particulate matter and microorganisms	The prepared solution is filtered through bacteria-retentive membrane filters (0.22 µm). Multiple filtration steps may be used for clarity.
4. Filling and Sealing	Transfer into final container	The sterile solution is filled into ampoules, vials, or bottles using automatic filling machines under aseptic conditions in a Grade A laminar airflow hood.
5. Sterilization	Ensure sterility	Depending on product stability: • Autoclaving (121°C, 15 psi, 15–20 min) for aqueous stable solutions. • Dry heat sterilization for oily products. • Filtration sterilization for heat-sensitive products.
6. Inspection	Ensure product quality	All sealed units are inspected visually for clarity, particulates, leaks, and defects. Automatic or manual inspection systems are used.
7. Labeling and Packaging	Final product handling	After inspection, products are labeled (name, strength, batch, expiry, storage) and packed in sterilized containers to prevent contamination.
8. In-Process and Final Testing	Quality control checks	Tests include sterility, pyrogen, pH, particulate, isotonicity, and assay tests before release.

Production Facilities and Environmental Controls

A. Facility Layout and Design

- To minimize contamination, parenteral manufacturing areas must be designed according to Good Manufacturing Practices (GMP) and WHO/FDA aseptic guidelines.

Key Areas in Parenteral Production:

1. Clean Room / Aseptic Area
    - For filling and sealing operations.
    - Maintained under HEPA-filtered laminar air flow.
    - Positive air pressure prevents entry of unfiltered air.
2. Change Rooms / Gowning Area
    - Personnel must wear sterile garments before entering aseptic zones.
3. Component Preparation Area
    - For washing and sterilizing containers, closures, and equipment.
4. Solution Preparation Area
    - For dissolving, mixing, and filtration of drug solutions under controlled conditions.
5. Sterilization Area
    - Houses autoclaves, dry-heat ovens, and sterilizing filters.
6. Filling and Sealing Area
    - Most critical area; operations performed under Grade A (Class 100) laminar air flow.
7. Quarantine and Storage Area
    - For storing finished products before and after quality approval.

B. Environmental Controls

Parameter	Controlled Value / Method	Purpose
Clean Air Supply	HEPA-filtered laminar flow (0.3 µm particle retention)	Remove airborne contaminants
Air Pressure	Positive pressure gradient	Prevent ingress of contaminated air
Temperature	20–25°C	Operator comfort and product stability
Relative Humidity	45–55%	Prevent microbial growth and electrostatic charges
Air Changes per Hour	20–40	Maintain clean air conditions
Surface Materials	Smooth, non-porous, easy to clean	Avoid dust accumulation
Personnel Hygiene	Sterile gowns, masks, gloves	Prevent microbial contamination

Aseptic Processing

- Aseptic processing refers to preparing, filling, and sealing sterile products under sterile conditions, without terminal sterilization of the final product.
- It ensures sterility throughout the process rather than relying on post-sterilization.

A. Steps in Aseptic Processing

1. Preparation of Components
    - Containers, closures, and equipment are cleaned and sterilized separately.
2. Preparation of Product
    - The bulk solution is prepared and sterilized by filtration (for heat-labile drugs).
3. Transfer to Aseptic Area
    - Sterile materials are transferred through sterile pass boxes or airlocks.
4. Aseptic Filling
    - The sterile solution is filled into sterile containers using aseptic filling machines under Grade A laminar airflow.
5. Sealing
    - Containers are immediately sealed with sterile closures to maintain sterility.
6. Terminal Handling
    - Products are inspected, labeled, and packed under clean but non-aseptic conditions.

B. Requirements for Aseptic Processing

Category	Requirements
Facility	Class 100 cleanroom, HEPA filters, laminar flow benches
Personnel	Highly trained, must follow aseptic gowning and hygiene
Equipment	Sterilized, validated, and regularly maintained
Environment	Temperature, humidity, and air pressure controlled

Monitoring	Regular microbiological and particulate testing

C. Advantages of Aseptic Processing

1. Suitable for heat-sensitive drugs (e.g., antibiotics, vitamins).
2. Maintains high product quality and stability.
3. Reduces risk of degradation during sterilization.
4. Allows flexibility in formulation and packaging.

D. Limitations of Aseptic Processing

1. High cost and complexity of facility setup.
2. Requires trained personnel and strict monitoring.
3. Risk of contamination if any aseptic break occurs.
4. Validation and environmental monitoring are critical and time-consuming.

E. In-Process Controls during Aseptic Processing

Control Parameter	Purpose
Sterility testing	Ensures freedom from microorganisms
Environmental monitoring	Detects microbial load in air/surfaces
Pressure differential	Prevents backflow of contaminated air
HEPA filter integrity test (DOP test)	Confirms filter performance
Personnel monitoring	Checks contamination by operators
Media fill test	Simulates aseptic filling to validate sterility maintenance

Formulation of Injections

- Injections are sterile preparations intended to be administered into the body by parenteral routes (e.g., intravenous, intramuscular, subcutaneous).
- They may be solutions, suspensions, or emulsions, or they may be dry solids that yield solutions or suspensions upon addition of a suitable vehicle.

Components of an Injection Formulation

Component	Function	Examples
Active ingredient (Drug)	Produces the desired pharmacological effect	e.g. Adrenaline, Insulin
Vehicle	Solvent or carrier for drug	Water for injection, oils, PEG
Buffering agents	Maintain pH for stability	Sodium phosphate, acetate buffer
Antioxidants	Prevent oxidation	Ascorbic acid, Sodium bisulfite
Preservatives	Prevent microbial growth (in multi-dose vials)	Phenol, Benzyl alcohol
Stabilizers	Improve product stability	Gelatin, PVP
Tonicity adjusters	Maintain isotonicity	Sodium chloride, Dextrose
Chelating agents	Bind trace metals that catalyze degradation	EDTA
Solubilizing agents	Enhance solubility of poorly soluble drugs	PEG 400, Propylene glycol, Polysorbate 80

General Steps in Formulation of Injections

1. Selection of vehicle and excipients
    - Based on solubility, stability, compatibility, and route of administration.
2. Preparation of solution/suspension
    - Drug and excipients dissolved or dispersed in the chosen vehicle.
3. Filtration
    - Clarification by membrane filters (0.22 μm) to remove particles and microorganisms.
4. Filling into containers
    - Performed under aseptic conditions in Grade A (Class 100) laminar flow hoods.
5. Sealing
    - Ampoules sealed by flame; vials sealed with sterile rubber stoppers and aluminum caps.
6. Sterilization
    - By autoclaving (121°C, 15 psi, 15–20 min) or by filtration (for heat-labile drugs).
7. Inspection and labeling
    - Checked for clarity, particulate matter, sterility, pH, and isotonicity.

Types of Injections

- Aqueous solutions: e.g., Dextrose Injection, Insulin Injection
- Non-aqueous solutions: e.g., Vitamin E Injection (in oil)
- Suspensions: e.g., Procaine penicillin injection
- Emulsions: e.g., Propofol injection
- Dry powders for reconstitution: e.g., Ceftriaxone sodium

Formulation of Sterile Powders for Injection

- Sterile powders are dry solid substances that are reconstituted with a sterile solvent (usually water for injection) before administration.
- Used for drugs that are unstable in aqueous solution during storage.

Desired Characteristics

- Free from microorganisms and pyrogens
- Rapid reconstitution
- Physically and chemically stable
- Uniform particle size and flow
- Easily soluble or dispersible in vehicle

Steps in Formulation

1. Preparation of Solution or Suspension
    - Drug dissolved or dispersed in sterile solvent (usually water for injection).
    - Filtered to remove particulates.
2. Sterilization
    - Filter sterilization (for heat-labile drugs) or aseptic preparation.
3. Filling
    - Sterile solution filled into vials aseptically.
4. Freeze-Drying (Lyophilization) or Vacuum Drying
    - Water is removed by sublimation (explained in section 4).
5. Sealing
    - Vials sealed with sterile rubber closures under aseptic conditions.
6. Labeling
    - Directions for reconstitution and diluent to be added must be clearly printed.

Common Examples

- Penicillin sodium
- Cefotaxime sodium
- Streptokinase

- Anti-cancer agents like Doxorubicin HCl (lyophilized form)

Formulation of Large Volume Parenterals (LVPs)

- Large Volume Parenterals are sterile solutions (>100 mL) intended for intravenous administration for fluid, electrolyte, or nutrient replenishment.
- They are single-dose, pyrogen-free, and contain no preservatives.

Characteristics of LVPs

- Sterile and isotonic
- Free from preservatives and pyrogens
- pH near physiological range (7.4)
- Particles-free, clear, and stable

Composition

1. Active ingredients: Dextrose, NaCl, amino acids, vitamins.
2. Vehicle: Water for Injection (WFI).
3. Additives: Electrolytes, nutrients (no preservatives).

Common Types of LVPs

Type	Purpose	Example
Fluid replenishment	Restore blood volume	Normal saline (0.9% NaCl)
Electrolyte replenishment	Correct electrolyte imbalance	Ringer's lactate
Carbohydrate solution	Provide calories	5% Dextrose injection
Amino acid solutions	Protein supplementation	Aminoven, Vamin
Fat emulsions	Energy source	Intralipid
Combination solutions	Nutrition and energy	Dextrose + Electrolyte infusion

Manufacturing Steps for LVPs

1. Preparation of solution
    - Dissolve ingredients in WFI with continuous stirring.
    - Filter through 0.45 µm or 0.22 µm membrane.
2. Deaeration
    - Removes dissolved gases to prevent oxidation.
3. Filling
    - Aseptic filling into large bottles or flexible bags.
4. Sealing
    - Bottles closed with sterile closures or heat-sealed bags.
5. Terminal Sterilization
    - By autoclaving at 121°C for 20–30 minutes.
6. Inspection
    - Check for clarity, particulates, volume, and leaks.
7. Labeling and Packaging
    - Clearly state composition, volume, storage, and route.

Containers Used

- Glass bottles (Type I borosilicate glass)
- Plastic bottles (polyethylene)
- IV infusion bags (PVC, non-PVC materials)

Formulation of Lyophilized Products

- Lyophilization (freeze-drying) is a dehydration process in which water is frozen and then removed by sublimation under vacuum.
- Used for heat- and moisture-sensitive drugs to increase stability and shelf life.

Objectives of Lyophilization

- Improve stability of thermolabile drugs.
- Facilitate rapid reconstitution before administration.
- Produce porous, uniform cake structure.
- Extend product shelf life.

Steps in Lyophilization Process

Stage	Description
1. Freezing	The solution is frozen at -40°C to -50°C, forming ice crystals.
2. Primary Drying (Sublimation)	Under vacuum, ice sublimes directly into vapor, leaving a porous cake.
3. Secondary Drying (Desorption)	Removes bound moisture at slightly higher temperature (20–40°C).
4. Sealing	The vials are sealed under vacuum or nitrogen to prevent moisture absorption.

Formulation Considerations for Lyophilized Products

Component	Purpose
Bulking agents	Provide structure and bulk to cake (e.g., mannitol, lactose).
Buffering agents	Maintain pH (phosphate, citrate buffer).
Cryoprotectants/Lyoprotectants	Protect drug during freezing (e.g., sucrose, trehalose).
Stabilizers	Maintain chemical integrity (PVP, gelatin).

Advantages of Lyophilized Products

1. Improved stability of thermolabile drugs.
2. Lightweight and easy to transport.
3. Rapid reconstitution before use.
4. Reduced microbial growth due to low moisture.

Disadvantages

1. Expensive process and equipment.
2. Long processing time.
3. Fragile product (needs careful handling).
4. Strict aseptic control required during manufacturing.

Examples of Lyophilized Products

- Antibiotics: Penicillin, Ceftriaxone
- Hormones: Oxytocin, ACTH
- Vaccines: BCG, Measles
- Enzymes: Streptokinase, Urokinase

Containers

Ideal Requirements of Containers

1. Should maintain sterility of product throughout shelf life.
2. Should not react chemically or physically with the formulation.
3. Should prevent loss of solvent by evaporation or diffusion.
4. Should withstand sterilization conditions (heat, pressure).
5. Should be non-toxic, non-adsorptive, and non-leachable.
6. Should permit easy inspection of contents (preferably transparent).
7. Should be compatible with the closure system and sealing method.

Types of Containers

Container Type	Description	Material	Use
Ampoules	Hermetically sealed small containers (1–30 mL)	Glass (Type I or II)	Single-dose injections
Vials	Small bottles with rubber closures and aluminum seals	Glass or Plastic	Single- or multi-dose injections
Infusion Bottles	Large bottles (100–1000 mL) for IV fluids	Glass Type I or plastic	Large Volume Parenterals (LVPs)
Plastic Bags / Bottles	Flexible containers for IV infusions	PVC or polyolefin	Disposable infusion packs
Pre-filled Syringes	Ready-to-inject sterile syringes	Glass or plastic barrel	Vaccines, insulin, emergency drugs

Types of Glass Used

Glass Type	Composition	Use
Type I (Borosilicate glass)	High resistance to thermal shock and chemicals	For all parenteral products, especially alkaline or sensitive drugs
Type II (Treated soda-lime glass)	Surface treated to improve resistance	For acidic and neutral aqueous solutions
Type III (Soda-lime glass)	Ordinary glass	For dry powders and non-aqueous products only
Type NP (Non-	Not for injections	Used for non-sterile oral

parenteral)		preparations

Closures

- Closures are used to seal the container, maintain sterility, and allow withdrawal of the contents without contamination.

1. Rubber Closures

- Made from butyl, bromobutyl, or silicone rubber.
- Used in vials and infusion bottles.

Requirements:

- Must be non-reactive, elastic, and compatible.
- Should re-seal after needle withdrawal.
- Must withstand repeated sterilization.

Types:

- Flanged type (used for serum vials)
- Plug type (used for lyophilized products)

2. Aluminum Caps

- Used to secure rubber closures on vials.
- May have flip-off seals or tear-off discs.

3. Plastic Closures

- Used for infusion bottles and plastic containers.
- Provide tamper-evident sealing.

Compatibility Considerations

- Closures should not absorb or leach chemicals into the product.

- Glass containers should not adsorb or catalyze drug degradation.
- Compatibility testing is done during preformulation studies.

Filling and Sealing of Ampoules, Vials and Infusion Fluids

Filling and Sealing of Ampoules

1. Filling

- Ampoules are washed, sterilized, and dried before use.
- Filling is done by vacuum filling, pressure filling, or syphon filling methods under laminar air flow (Grade A).
- Volume ranges from 1 to 30 mL.

2. Sealing

- Immediately after filling, the neck of the ampoule is melted by flame (gas or oxygen flame).
- Tip-seal or pull-seal methods are used:
  - Tip-seal: Ampoule tip is melted and sealed.
  - Pull-seal: Ampoule neck is drawn out and sealed.

3. Post-sealing

- Ampoules are washed externally, sterilized (if needed), and inspected for leaks, cracks, or glass particles.

Filling and Sealing of Vials

1. Filling

- Sterilized vials are filled aseptically using automatic volumetric filling machines.
- Performed under laminar flow conditions.

2. Stoppering

- Immediately after filling, sterile rubber closures are partially inserted using stoppering machines.

3. Sealing

- After sterilization or lyophilization, aluminum caps are crimped over the rubber stoppers to seal the vials hermetically.

4. Labeling

- Vials are labeled with product name, strength, batch number, and storage conditions.

Filling and Sealing of Infusion Fluids

1. Preparation

- Large volume parenteral solutions are prepared in stainless steel tanks using Water for Injection (WFI).
- Solutions are filtered (0.22 µm) to ensure clarity.

2. Filling

- Filled aseptically into glass bottles or plastic bags (100–1000 mL).
- Filling machines operate in a Grade A clean room.

3. Sealing

- Glass bottles: Closed with rubber closures and sealed with aluminum caps.
- Plastic bags: Heat-sealed or welded to ensure tightness.

4. Sterilization

- Terminal sterilization in autoclave at 121°C for 20–30 minutes.

5. Inspection

- Each container is visually inspected against black and white backgrounds for clarity, particulates, and volume.

Quality Control Tests for Parenteral Products

Test	Purpose
Sterility test	Ensure freedom from microorganisms
Pyrogen test (LAL test)	Detect pyrogenic substances
Particulate matter test	Check clarity and cleanliness
pH test	Maintain physiological compatibility
Isotonicity test	Ensure osmotic balance with body fluids
Assay of drug content	Ensure correct strength
Leak and integrity test	Detect leaks in containers

A. Sterility Test

- Purpose: Ensure the product is free from viable microorganisms.
- Method:
  - Direct inoculation method
  - Membrane filtration method
- Media used: Fluid thioglycollate medium (anaerobic bacteria) and soybean–casein digest medium (aerobic bacteria).
- Incubation: 14 days at 20–35°C.
- Result: No microbial growth = passes the test.

B. Pyrogen Test / Bacterial Endotoxin Test

1. Rabbit Test

- Inject test sample into rabbits and record temperature rise.
- If rise < 0.6°C → passes.

2. Limulus Amebocyte Lysate (LAL) Test

- Enzymatic test using extract from horseshoe crab blood cells.
- Detects bacterial endotoxins.
- Preferred modern method due to accuracy and animal-free nature.

C. Particulate Matter Test

- Detects presence of visible or sub-visible particles in injections.

Methods:

1. Visual inspection: Against contrasting background.
2. Light obscuration test: Counts sub-visible particles using an electronic particle counter (e.g., HIAC system).

Limits (as per IP/BP):

- For injections <100 mL:
  - ≥10 µm → ≤6000 particles
  - ≥25 µm → ≤600 particles

D. pH Determination

- pH should be within the physiological range (6.5–7.5) or as specified.
- Measured using a pH meter.

E. Isotonicity Test

- Ensures osmotic pressure equal to that of body fluids (~0.9% NaCl).
- Adjusted using cryoscopic or NaCl equivalent method.
- Prevents hemolysis or pain at injection site.

F. Assay of Active Ingredients

- Ensures correct potency and drug content.
- Performed by HPLC, UV spectrophotometry, or titration.

G. Leakage Test

- Checks integrity of sealed ampoules and vials.
- Ampoules immersed in dye solution and subjected to vacuum; presence of dye inside indicates leak.

H. Other Tests

- Extractables and leachables test (for containers).
- Closure integrity test (for vacuum-sealed products).
- Weight variation test (for filled volume accuracy).