


PARANTERALS

LAB -8-

Parenterals are dosage forms and therapeutic agents that are free from micro-organisms. They belong to a large category (sterile products that include parenterals, ophthalmics, and irrigating preparations).

They considered unique among other dosage forms since they are injected through the skin or mucus membrane into the internal body compartments, so they must be free from microbial contamination and from toxic components as well as posses high level of purity.

Pharmacologically parenterals can be divided into:

1- Solutions ready to be injected.

2- Dry soluble materials reconstituted prior use.

3- Dry insoluble materials reconstituted prior use.

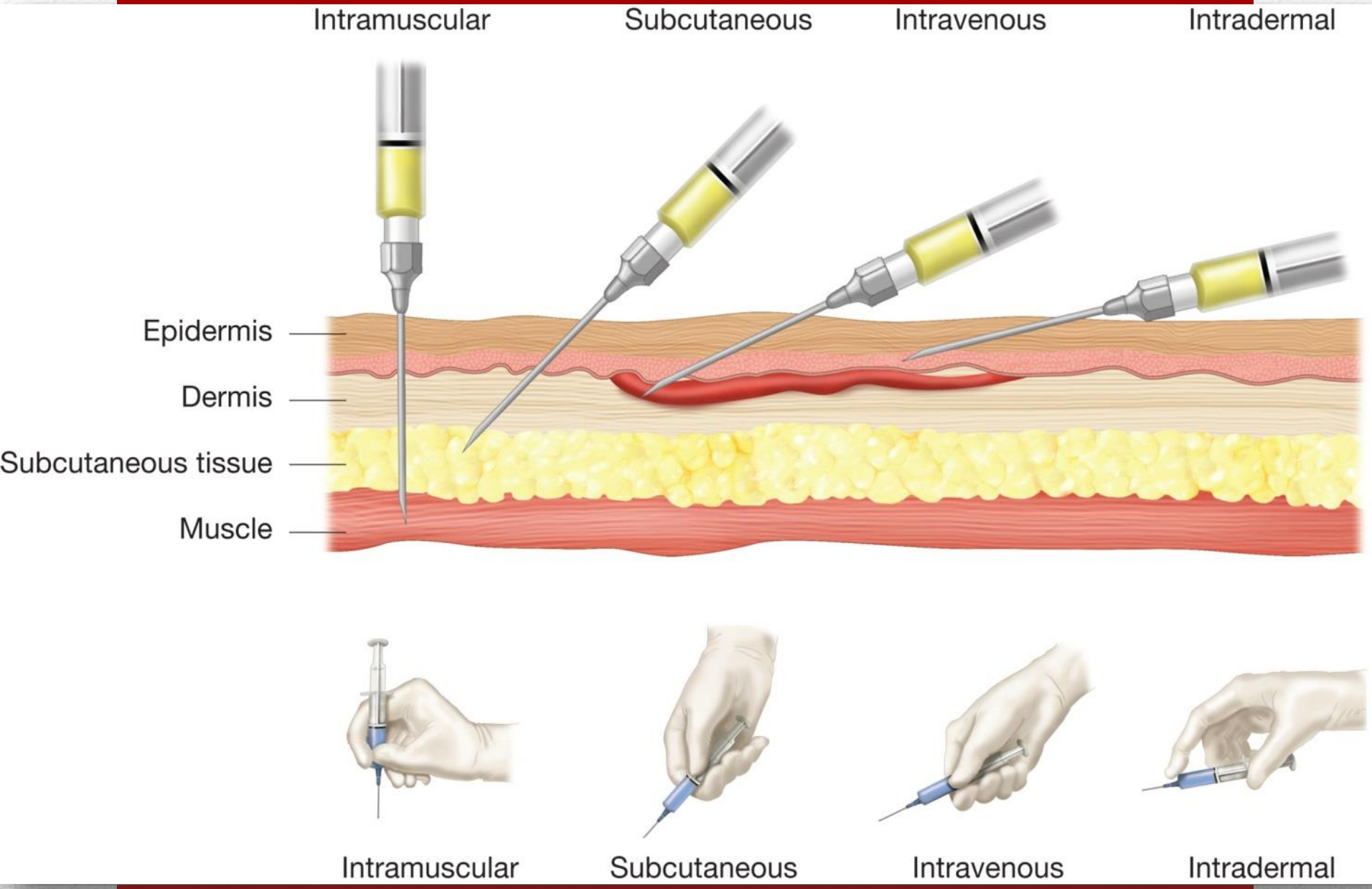
4- Suspensions ready to be injected.

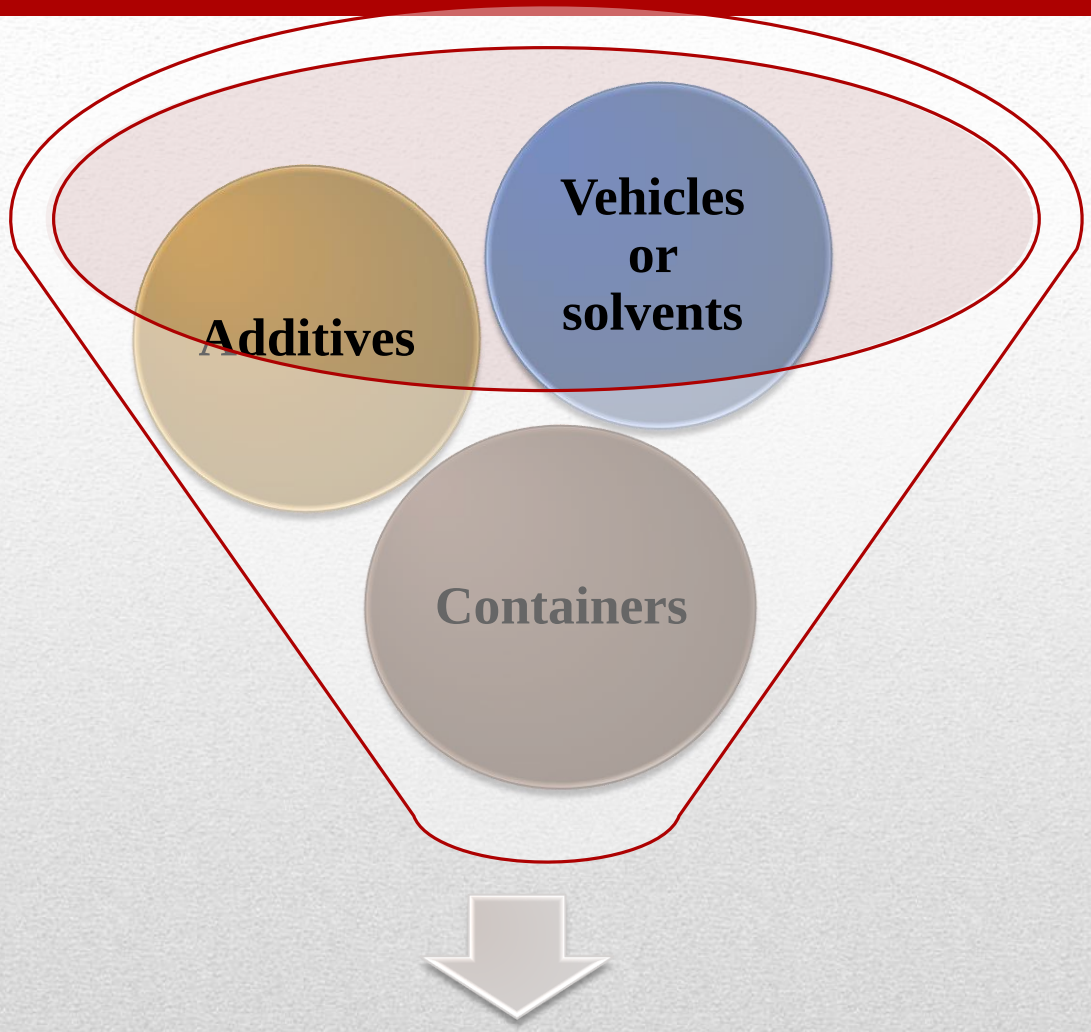
5- Emulsions which are used mostly for lipid supplements, nutrients, but now not used because the main problem in the formulation of parenteral emulsions is the attainment and the maintenance of uniform oil droplet which should be of 1-5 microns in size as the internal phase.

All these preparations require **high** level of **purity** of **all ingredients** as well as **freedom** from **chemical**, **physical** (**particles**), **microbial contaminants**, and **pyrogen free** (**as indicative of a microbiologically clean process**).

They usually require **buffers** to stabilize the pH of the product, and **additives** to keep them **isotonic**, as well as **stabilizers** such as **antioxidants**.

Routes for administration for parenteral preparations includes **intravenous**, **intramuscular**, **subcutaneous** (**hypodermic**), **intradermal**, **intrathecal or intraspinal** (**in the cerebrospinal fluid**).


Intramuscular
Subcutaneous
Intravenous
Intradermal
Epidermis
Dermis
Subcutaneous tissue
Muscle
Intramuscular
Subcutaneous
Intravenous
Intradermal



Formulation of parenterals

(1) Vehicles or solvents:

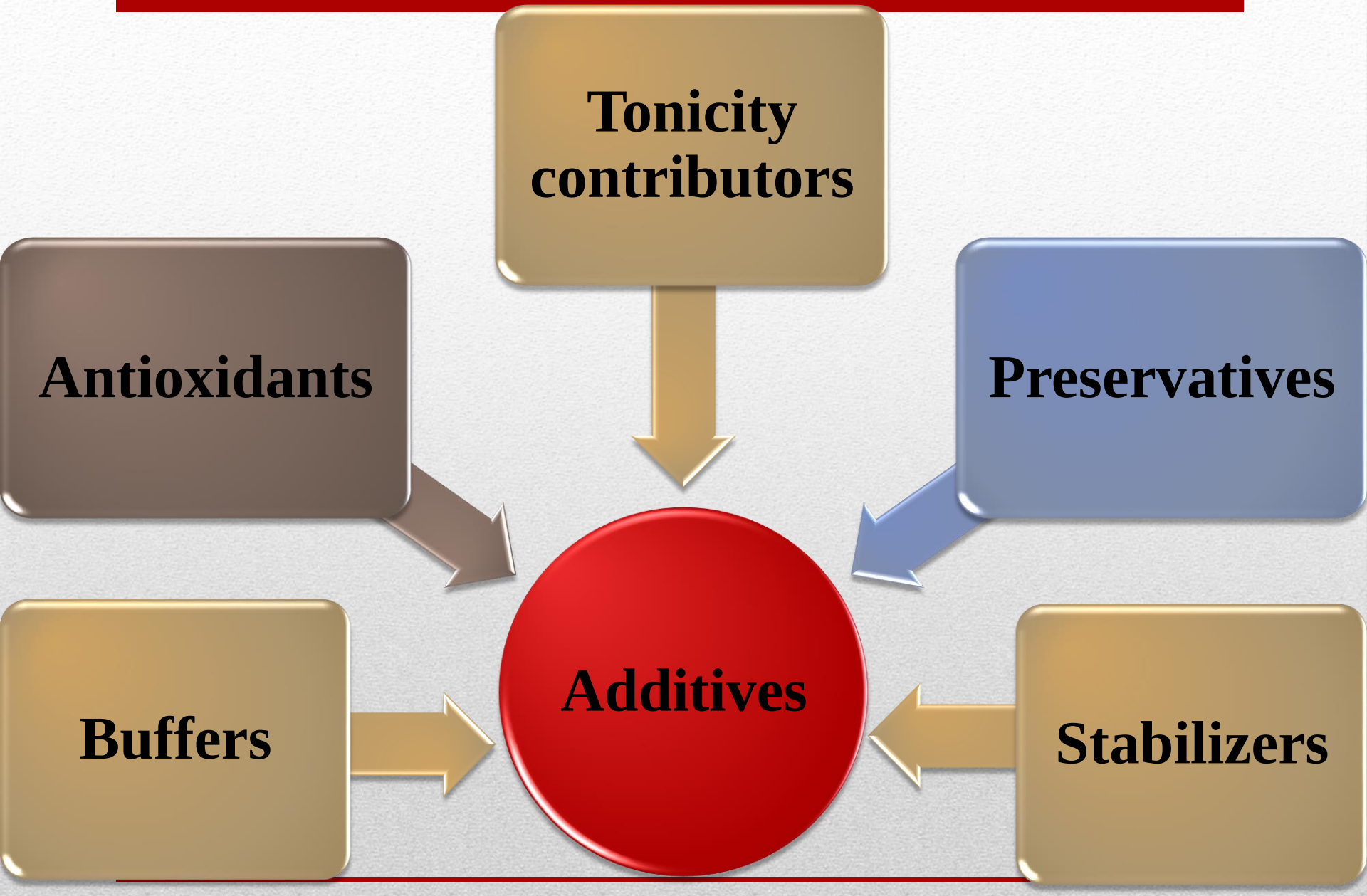
- The solvents suitable for sterile products are limited to those that produce a **little or no tissue irritation** which could be either **aqueous (water) solvents or non-aqueous solvents.**

Aqueous (water) solvents

The water is the most common since it's the vehicle for all natural body fluids. This water must be purified, pyrogen free, and sterile.

non-aqueous solvents

Sometime it's necessary to eliminate water entirely or in part from the vehicle primarily because of solubility factors or hydrolytic reactions, so the used solvents must be non-toxic, non-irritant, and do not cause sensitivity and do not exert adverse effects on the ingredients of the formulation.


Tonicity contributors
Antioxidants
Preservatives
Additives
Buffers
Stabilizers

(2) Additives:

A variety of ingredients may be added to a formulation to provide the required stability and therapeutic efficacy, they include:

A- Buffers: Like **acetate, citrate, and phosphate**, these added to **maintain the required pH** for many products and **to decrease slight differences in pH** that may occur.

- The **pH** of the injectable required **for maximum solubility may not** be that **for maximum stability**, so **a balance pH** must be achieved to **maintain maximum solubility and stability.**
- The **buffer** systems are selected with consideration of **their effective pH range, concentration**, and **their chemical effects to the total product**.

B- Antioxidants: these are included in many formulations to **protect the therapeutic agent from oxidation** particularly under accelerated conditions of thermal sterilization.

- Note: For products in which the oxygen enters degradation reactions, an antioxidant effect can be achieved by **displacing air (O_2)** from the container with the product, this can be accomplished by **saturation of the liquid with either N_2 or CO_2** and **sealing** of the final product **after displacing the air** from the product **with gas.**

C- Tonicity contributors: Which are compounds that contributing to the **isotonicity** of a product **to reduce the pain of injection** in areas with nerve endings. The **buffers** may act as **tonicity contributors as well as stabilizer for the pH.**

D- Preservatives: The type used depends on the **type of the vehicle** used and it's may be an **antibacterial agent** in a **bacteriostatic** concentration which included in the formulation of the products packaged in **multiple doses vials**, for example **benzyl alcohol, benzylkonium chloride, and chlorobutanol.**

E- Stabilizers: Like **EDTA**, the stabilizer serve the same effect as the **antioxidant**, also it may be added **to prevent the leaching of the ferrous that is present in amber vials and ampoules** to the constituents.

- These added substances may be **solubilizers** like **dimethylacetamide, ethyl alcohol, glycerin, lecithin, povidone.**

- They also may include **antioxidants, chelating agents, buffers, tonicity contributors, antibacterials, antifungals, hydrolysis inhibitors, antifoamings** and others for specialized reasons.

These substances must be:

1- **Non-toxic** in the quantity administered to the patient.

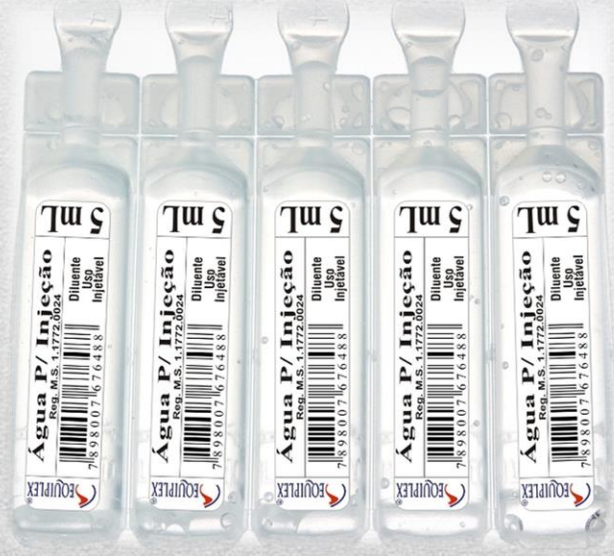
2- Do **not interfere** with the **therapeutic efficacy.**

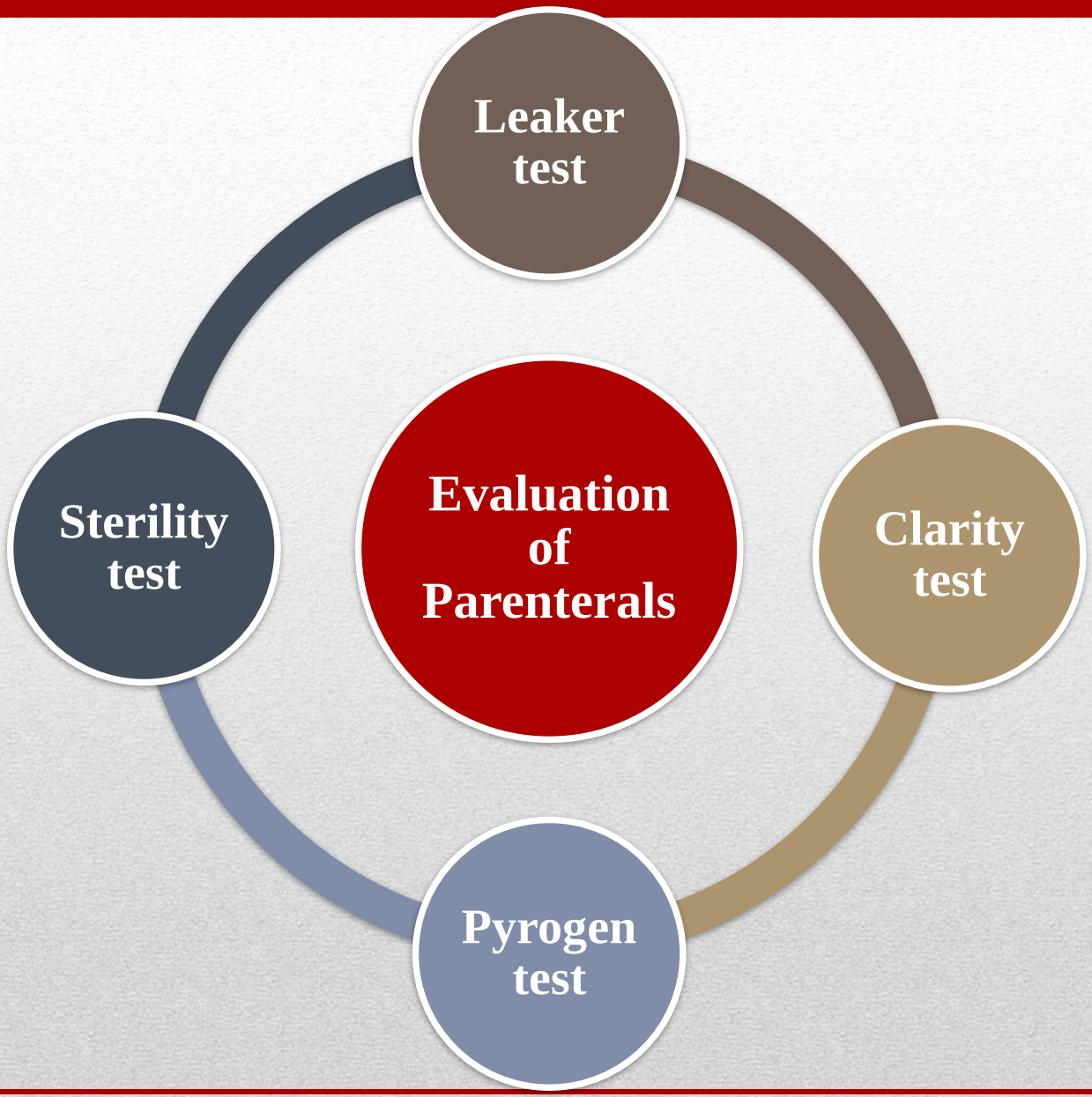
3- Do **not interfere** with the **assay of the active ingredient.**

4- Must be **active** and present when needed throughout the **life of the product**.

(3) Containers: They must be **inert**, **non-toxic**, **easy transport**, **easy sterilize, and easily cleaned**.

- We have 2 types **plastic and glass containers**, and each has advantages and disadvantages.




Leaker test
Clarity test
Pyrogen test
Sterility test
Evaluation of Parenterals

- **1- Leaker test:** is mainly used to determine the **efficiency of the sealing** so the incompletely sealed ampoules may be discarded, this is detected by producing a **negative pressure within completely sealed ampoule usually in a vacuum chamber, while the ampoule is entirely submerged in deeply colored dye solution usually 0.5-1% methylene blue, then the subsequent atmospheric pressure will cause the dye to penetrate any opening, thus make it visible after washing the ampoule to clear it from the dye.**

- The **vials and bottles** are **not subjected to leaker test** because the **rubber closure is not rigid**, also **capillaries of about 15 microns in diameter or smaller may not be detected** by this test, also this test is used for **colorless solutions and clear containers**.

2- Clarity test: This is done by **visual inspecting** of each **externally clean containers under a good light**, **baffled against reflection into the eyes and viewed against a black and white background with the contents set in motion with a swirling action**. A moving particle is much easier to see than the one that is stationary, but the **care** must be exercised **to avoid introducing air bubbles** which are **difficult to distinguish from dust particles**. The **human** inspector is **subjected** to **reduction in efficiency** by eye **strain, fatigue, emotional disturbances** that's why **instrumental methods more accurate** which **depends on the principle of light scattering, light absorption and electrical resistance** and these **used to obtain particle count and size distribution.**

3- Pyrogen test: The **pyrogens are products of the metabolism of the microorganism** which will produce rising in body temperature 1 hour after injection.

- This test is done by **injecting the sample in the vein of 6 rabbits** and **observe the temperature** of the rabbits for **3 hour period by the means of rectal thermometer, if the temperature increases** then the product **is contaminated and should be rejected**, **while if only 1 rabbit temperature increased** so perform the test with **additional 6 rabbits** and **only 1 rabbit temperature increase out of 12 rabbits** is **allowed, thus more than 1 rabbit the product will be unaccepted**.

4- Sterility test: After the **sterilization step** a **sample** is taken and **inoculated on agar, incubated at 37° C for 14 days then observe if any growth developes**.

Note: The **autoclave** is used to ensure the sterilization process occurred completely, by **utilizing a specific tube as brown color that turns into blue color when sterilization is completed**.

types of sterilization process

1- Physical sterilization: which is either **thermal** such is **dry heat, oven, moist heat, or autoclave**, and **non-thermal** methods such as **UV light, filtration, ionizing radial light**.

2- Chemical sterilization: with the utilization of certain **chemical agents** such as **ethylene oxide.**

Note: the choice of the **proper type of sterilization** process **depends** on the **physico-chemical properties of the drug**, the **type of the container** as **vial or ampoule** since in vial the rubber is affected by heat.

The area of preparation of injection must have these properties:

1-Aseptic Area

2- Isolated Area

3- Circulated with filtered air to remove the dust and bacteria.

4- Easily cleaned and sterilize

5- No large holes are present.

6- Working people must ware certain clothing.

Thank You