Drug Packaging

I. DEFINITION:

Packaging is the set of items surrounding the pharmaceutical form from its manufacture to its use. Pharmaceutical packaging can refer to an operation complementary to the formulation process.

II. ROLES:

- Protective Role: To ensure the preservation of the drug until the moment of use against external factors (humidity, light, air), biological contamination, physical damage, and counterfeiting.
- Functional role: Designed to facilitate the use of the medication. It can also influence its effectiveness. - Safety element: Increases the safety of its use. Examples: child-resistant packaging, tamper-evident closures.

- Identification and information role: This includes labeling and instructions.

- Marketing role: The choice of design, logos, and colors is a marketing decision aimed at satisfying the patient.

III. REQUIRED QUALITIES FOR PACKAGING MATERIALS AND ITEMS:

- Sufficient physical resistance, while remaining lightweight and compact.

- Impermeability to the drug's components and external agents (air, humidity, etc.).

- Chemical inertness with respect to the contents (dissolution or chemical reactions).

- Absolute safety.

- Suitability for various industrial processes (hot molding, etc.).

- Relatively low production cost.

- Measures in place to combat counterfeiting.

IV. DIFFERENT TYPES OF PACKAGING:

Depending on the level of contact with the formulation, we distinguish:

1. Primary packaging: This is "the container or any other form of packaging with which the medication comes into direct contact." This is the most delicate packaging phase. Its selection is guided by the nature of the contents (liquid, paste, solid), its compatibility, and its stability with the packaging materials.

2. Secondary packaging: This is generally represented by the carton. This type of packaging is not in direct contact with the medication but protects it. It may include several primary packagings (blisters), accessories, and a leaflet. Paper and cardboard are widely used for this outer packaging (lightweight and inexpensive). It serves as a medium for indications but also as a marketing tool.

3. Tertiary packaging: This is the final packaging stage before shipment to customers (wholesalers/distributors, pharmacies). It includes: possible bundling of the packaging II and grouping into crates for transport. The crates are then grouped onto pallets.

V. MATERIALS & PACKAGING:

V.1. GLASS & GLASS PRODUCTS:

The primary material used in pharmaceuticals, due to its unique properties (hardness, transparency, stability, chemical inertness, etc.), despite its drawbacks (fragility, high density, bulkiness, etc.). Chemical Composition: Based on silica, glass can be combined with the following elements: $(SiO_2)_m$ $(Na_2O)_n$ $(CaO)_p$ Vitrifying agent Flux Stabilizer These three main components can be partially replaced or combined with various elements that give them specific properties. For example: - B_2O_3 partially replacing SiO_2 reduces the coefficient of expansion and results in a glass that is less fragile to temperature variations and more neutral. - The presence of K_2O increases the glass's brilliance. Structure: Glass has a semi-organized amorphous structure. The eventual transition to a crystalline state results in devitrification. Physical Properties of Glass:

-Fragility to temperature variations is explained by a high coefficient of thermal expansion and low thermal conductivity. This heat fragility is even greater the thicker the glass.

-Transparency to visible light allows for assessing the clarity of solutions and observing changes in the appearance of the medication (stability). In some cases, it is advantageous to protect the container from light.

Chemical properties of glass: As glasses are mineral silicates, organic products have practically no effect on them. However, they are attacked by mineral reagents: with water and acids, there is only an exchange of cations, while with bases the glass is slowly and completely destroyed. Different types of glass used in pharmacy: Concept of resistance

Hydrolytic resistance: "This is the resistance offered by glass to the release of water-soluble mineral substances under specific contact conditions between the inner surface of the container or the glass grains and the water." This hydrolytic resistance is assessed by measuring the alkalinity released. Based on this resistance, four classes of glass are distinguished: I, II, III, and IV.

Class I glasses:

Neutral throughout, represented by borosilicate glasses. With high hydrolytic resistance, they do not release any elements (soluble or insoluble). Suitable for most aqueous preparations for parenteral or non-parenteral use.

Class II glasses:

Calcium-based glasses with surface treatments to increase their hydrolytic resistance. They release few bases. Suitable for acidic and neutral aqueous preparations for parenteral or non-parenteral use.

Class III glasses:

Medium hydrolytic glass. Suitable for preparations in non-aqueous vehicles for parenteral use, powders for parenteral use, and preparations for non-parenteral use.

Class IV glasses:

Low hydrolytic glass. Suitable for solid preparations and certain liquid or semi-solid preparations for non-parenteral use. Note: Only Class I glass containers are reusable.

V.2. PLASTICS & PLASTIC ARTICLES:

These are organic products resulting from the more or less frequent repetition of a monomer. The bonds within the polymer can be linear or branched (covalent or secondary bonds). These bonds determine the two main properties of plastics: plasticity and elasticity. We distinguish: - Thermoplastic polymers, which become sufficiently fluid upon heating to allow molding.
- Thermosetting polymers do not soften when heated, so the process is designed so that polycondensation is completed within the mold. The main types of plastic are:

1. Thermoplastics:

1.1. Polyethylenes (PE): This is the most widely used plastic in packaging. Their properties vary with the degree of crystallinity, molecular weight, and branching. Two types are distinguished: - Low-density polyethylene (LDPE): Sensitive to temperatures > 80°C. - High-density polyethylene (HDPE): Sensitive to temperatures > 115°C. HDPE is less permeable and more resistant, but it is less flexible and less transparent than LDPE. It is used to make: flexible-walled bottles (powders, sprayers, droppers, etc.), rigid containers, tubes for tablets and powders, tubes for ointments, molds and packaging for suppositories, syringes, etc.
1.2. Polypropylene (PP): Polypropylene is used, but on a much smaller scale. Its properties are similar to those of PE, but it is more temperature-resistant (up to 150°C ◊ sterilizable by moist heat). It can be used to make films and rigid containers. It is the most commonly used plastic for syringes.

1.3. Polyolefins: Obtained by polymerizing ethylene or propylene, or by copolymerizing these with carboxylic acids or esters.

1.4. Polyvinyl chloride (PVC): This is a rigid material that can be worked like a light metal. With the addition of plasticizers, it becomes a more flexible material suitable for many uses. It is used in sheets for tubes, sachets, boxes, bottles, aluminum/PVC blisters, etc., or for bags for injectable solutions and flexible tubing for infusions.
1.5. Polystyrene: This is a fairly hard, rigid material that resembles glass but is much lighter, easily colored, and inexpensive. However, it is fragile and not heat-resistant, therefore not sterilizable. Used for boxes, rigid tubes, and bottles.

1.6. Polyamides: These have good mechanical properties, good thermal resistance, and allow for vacuum packaging.

1.7. Cellulose derivatives: Used mainly as packaging films, overwrap, and shrink wrap (regenerated cellulose, nitrocellulose, cellulose acetate, etc.).

1.8. Silicones: Used for sealing, as surface coatings, and for waterproofing glassware.

2. Thermosetting materials: Phenolics and aminoplasts. These are mainly used as packaging accessories for sealing. They are also used in coatings and are components of certain glues and adhesives.

V.3. ELASTOMERS & ELASTOMER PRODUCTS:

During their preparation, these undergo a treatment designed to reduce their plasticity and increase their elasticity. They are primarily used as packaging accessories and various other items: bottle caps, closure seals, baby bottle nipples, tubing and fittings for blood transfusion equipment, probes, etc.

• Natural Rubber: Extracted from the latex of certain plant species. It is not possible to obtain pure natural rubber; it always contains impurities that are difficult to remove without simultaneously eliminating the natural antioxidants.

• Synthetic Rubbers: More resistant to aging, the range of synthetic rubbers is extremely large due to the various possible combinations of monomers and additives (the most common being butyl, chlorobutyl, and nitrile rubber). This poses significant challenges for the analysis and quality control of these rubbers.

• Silicone rubbers: Their advantages are their stability in heat, cold, and ozone, and their hydrophobicity.

D. METALS & METAL PRODUCTS:

Aluminum is the most widely used metal in packaging (others are less common: tin, lead, stainless steel) thanks to its lightness, malleability, chemical resistance (it quickly forms a protective layer of alumina on the surface), impermeability to odors and gases, opacity to light and UV radiation, and its reflective properties which protect against heat. Uses: Pressurized packaging, alone or in combination in blister packs, suppository molds, ointment tubes, etc.

V- GENERAL TESTS OF PACKAGING MATERIALS

1- Identification: - Plastics and elastomers: Complex identification. - Mineral elements: Easy identification and quantification after calcination. - Organic additives: Performed on extracts with pure, acidic, or alkaline water, or with organic solvents.

2- Mechanical tests: Verify that the packaging is suitable for protecting the medication. - On the material or container: Tensile or elongation tests, hardness tests, and tests of resistance to tearing, bursting, impact, and crushing. - On the caps: Puncture test, fragmentation test, self-sealing test (in the case of multidose containers).

3- Permeability tests of plastics: Permeability to water vapor, gases (O_2, CO_2, air), volatile substances (solvents, gasoline, etc.), and liquids.

4- Chemical resistance tests: Predicting the tendency of packaging materials to undergo discharge phenomena when liquids (chosen according to the container's intended use) are placed in direct contact with the container. Example: "Hydrolytic resistance test of glass" - The bottles to be tested are treated with purified water, then filled to 90% of their capacity and placed in an autoclave for 1 hour at 120°C. - The alkalinity imparted to this water is titrated. - This test does not differentiate between type I and II glass; therefore, the containers are treated with a hydrofluoric acid solution, which removes the neutralized glass layer on the surface, and then the test is repeated.

5- Transparency: Verification of the clarity and proper preservation of the contents, and confirmation of the drug's protection against radiation by measuring transmittance using a spectrophotometer.

6- Safety testing: Cytotoxicity, acute or chronic systemic toxicity…

7- Shelf life (stability) testing: Exposing the drug in its packaging intended for marketing to various climatic conditions and verifying that its quality is maintained.