These **maximum BUDs** are recommended for **non-sterile compounded** drug preparations in **the absence of stability information** that is applicable to a specific drug or preparation.

USP CHAPTER <795> PHARMACEUTICAL COMPOUNDING— NON–STERILE PREPARATIONS

DOSAGE FORM	BUD
Non-aqueous formulations	No later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.
Water-containing oral formulations	No later than 14 days when stored at controlled cold temperatures
Water-containing topical/ dermal and mucosal liquid and semi-solid formulations	No later than 30 days.

Proper Packaging, Labeling and storage of pharmaceuticals: are all essential for providing adequate **product stability** and **efficacious use.**

Containers:

- According to USP, a **container is** "that which **holds the article** and is **or in direct contact with article**." The immediate container is "that which is in direct contact with the article at all times."

- The closure is part of the container

❖ Depending on the intended use and type of container, among the **qualities tested** are the following:

• Physicochemical properties.(eg. sorption of diazepam onto low density plastics)
• Light transmission for glass or plastic
• Drug compatibility
• Vapor transmission for plastics
• Leaching and/or migration
• Moisture barrier
• Toxicity for plastics
• Valve, actuator, metered dose, particle size, spray characteristics, and leaks for aerosols
• Sterility and permeation for parenteral containers
• Drug stability for all packaging

The USP classifies containers according to **their ability to protect their contents from external conditions** of handling, shipment, storage, and distribution:

Containers

well-closed

- protects contents from solids and from loss under ordinary conditions.

Tight-closed

- protects contents from contamination by **liquids**, **solids** or **vapors**, or evaporation under the ordinary conditions
- It is capable of tight re-closure

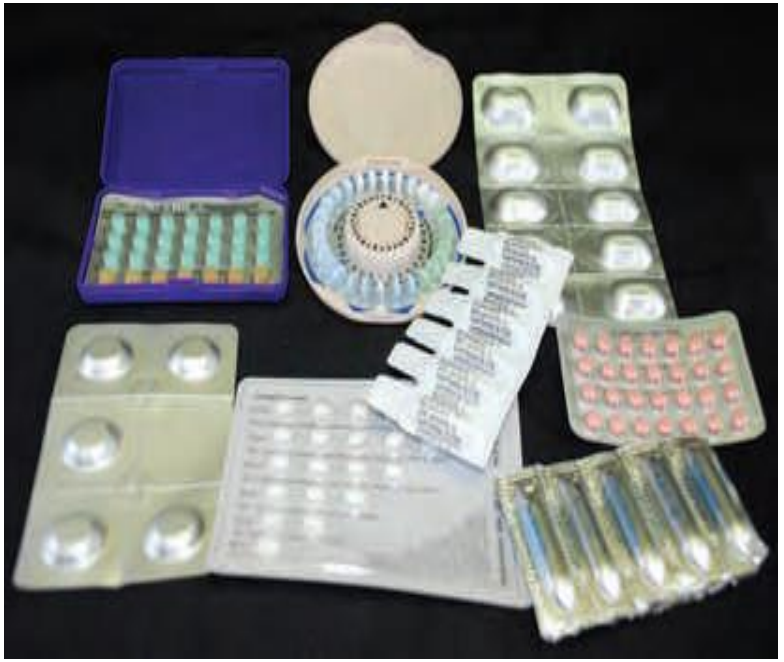
Hermetic

- is impervious to **air or any other gas** under the ordinary conditions.
- **Sterile hermetic containers** hold preparations intended for injection or parenteral administration

❑ **Unit-dose package (single-dose): (Avantages)**

positive identification of each dosage unit and **reduction of errors**, **reduced contamination** of the drug, **greater ease of inventory control** in pharmacy and nursing station, and **better management** and **less discarded medication** .

- The packaging materials may be combinations of paper, foil, plastic, or cellophane.
- The packaging of **solid dosage forms** in clear **plastic** or **aluminum blister** wells is perhaps the most popular single-unit packaging



Blister packaging of pharmaceuticals

- **Single-dose container:** when opened, cannot be resealed with assurance that sterility has been maintained.

- These containers include **fusion sealed ampoules** and **prefilled syringes and cartridges**.

- **Multiple-dose container:** is a hermetic container that **permits withdrawal of successive portions** of the contents **without changing** the strength or quality or purity of the remaining portion. These containers are commonly called vials.

- **Oral liquids** may be dispensed in single units in paper, plastic, or foil **cups** or prepackaged and dispensed in **glass containers** having threaded caps or crimped aluminum caps.

- **disposable plastic oral syringes** with rubber or plastic tips on the orifice for closure

- Other dosage such as, suppositories, powders, ointments, creams, and ophthalmic solutions, are also commonly found in single-unit packages.

❑ Unit–of- use packaging :

The quantity of drug product prescribed is packaged in a container Ex: if certain antibiotic capsules are prescribed to be taken 2 times a day for 10 days, unit-of-use packaging would contain 20 capsules. Other products may be packaged to contain a month's supply, such packaging "**Compliance packaging**" useful for **patients** taking **multiple medications**

❑ Light-resistant containers

- ✓ **Amber glass** or a light-resistant **opaque plastic** will reduce light transmission sufficiently to **protect** a **light-sensitive pharmaceutical**.
- ✓ **Ultraviolet absorbers (ex Tinuvin®)** may be added to transparent plastic to decrease the transmission of short ultraviolet rays.
- ✓ USP standards that define the acceptable limits of light transmission at any wavelength between 290 and 450 nm.

Recently, plastic packaging is the **coextruded two-layer high-density polyethylene (HDPE) bottle**, which has an **inner layer** of **black polyethylene coextruded** with an **outer** layer of **white polyethylene**. Increasingly being used in packaging of tablets and capsules. The container provides: **light resistance** and **moisture protection**.

- **Child-resistant & adult-senior use packaging**

a container that is fitted with a closure that is significantly difficult by children under 5 years of age to open or to obtain a harmful amount of its contents within a reasonable time and that is not difficult for “normal adults” to use properly

Material Used For Manufacture Of Containers

There are mainly four types of material: glass, plastic , metal and rubber.

Glass **used in packaging pharmaceuticals** are four categories :

Types I, II, and III intended for **parenteral products**, and type **IV: NP** is intended for other products.

- Each type tested according to resistance to water attack.
- Degree of attack is determined by **amount of alkali released** from glass in specified test conditions.
- leaching of alkali from glass to preparation could alter by pH and stability of product.
- **Type I** is **most resistant glass** of 4 categories.

Constitution and description of official glass types

Glass type	General description	Uses
TYPE 1	Highly resistant borosilicate glass	For buffered and unbuffered aqueous solutions, powders
TYPE 2	Treated (sulphur dioxide fumes) soda lime glass	For buffered aqueous solution with pH below 7 and for dry powders
TYPE 3	Soda lime glass	For dry powders and oleaginous solutions, not for aqueous preparations
TYPE 4	General purpose soda lime glass	Not for parenterals and for suspension and emulsion

Today, most products are packaged in **plastic**.

 intravenous fluids, plastic ointment tubes, plastic film-protected suppositories, and plastic tablet and capsule vials.

❖ The widespread use of **Plastic** containers arose from a number of factors:

1. The preference of plastic over glass due to: **Lightness weight** and **resistance to impact**, which **reduces transportation cost** and **losses** due to container damage

2. Versatility in container design, consumer acceptance
3. Consumer preference for plastic squeeze bottles in administration of ophthalmic, nasal sprays, and lotions
4. The popularity of blister packaging and unit-dose dispensing.

The physical and chemical alteration of the packaging material by the drug product is called modification. Example

polyethylene + **methyl groups** to every other carbon atom → **Polypropylene (can be autoclaved)**

Polyethylene —**chlorine** atom is added to every other carbon→ **Polyvinyl chloride** (PVC)

PVC is **rigid and has good clarity**, making it particularly useful in the **blister packaging** of tablets and capsules. However, it has a significant drawback for packaging medical devices (e.g.,syringes): it is **unsuitable for gamma sterilization**.

Among the newer plastics are **polyethylene terephthalate** (PET), **amorphous polyethylene terephthalate** glycol (APET), and polyethylene terephthalate glycol (PETG). Both APET and PETG have excellent **transparency** and can be **sterilized with gamma radiation.**

Among **problems** encountered in the use of **plastics** in packaging are:

(a) **Permeability of containers to atmospheric oxygen and moisture vapor**

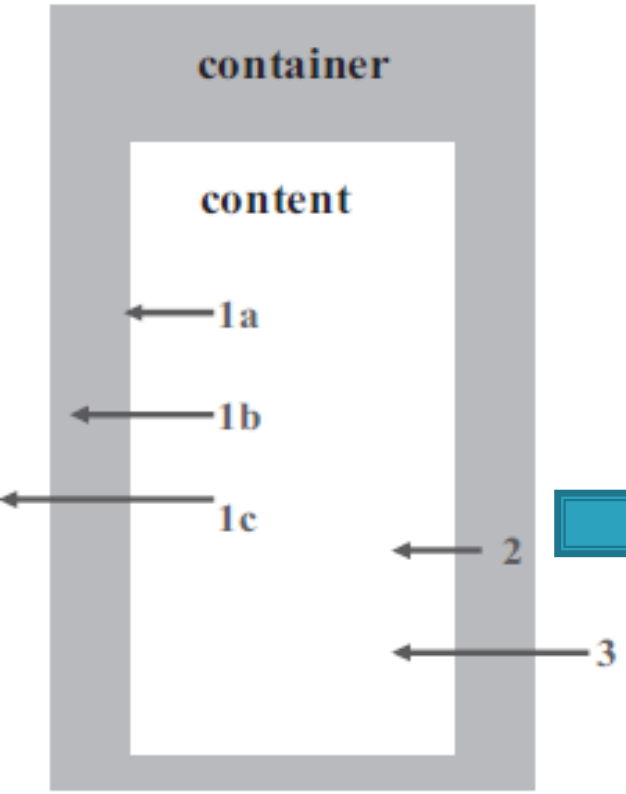
(*b*) **leaching** of the constituents of the container to the internal contents

(*c*) **absorption** of drugs from the contents to the container

(*d*) Transmission of light through the container

(*e*) Alteration of the container upon storage.

❖ Agents frequently added to alter the properties of plastic include **plasticizers**, **stabilizers**, **antioxidants**, antifungal agents, colorants, and others



(1a adsorption,
1b absorption),
1c permeation

2 leaching (release)
3 permeability

- **decrease of the activity** due to an adsorption of **the active substance**
- **active ingredient degradation** due to released substances
- content **precipitation**
- **pH change** due to a leaching of the material components
- **appearance change** (color) due to a leaching of the material components
- **analytical interference** during the determination of the active ingredient
- **safety change** due to a leaching of the material components

- The **permeability of a plastic is a function of**:

1. Nature of polymer;

2. the amounts and types of plasticizers, fillers, lubricants, pigments and other additives;

3. pressure; and temperature.

Increases in temperature, pressure, and the use of additives tend to increase permeability of plastic. Glass containers are less permeable than plastic containers.

- Many products liable to deteriorate in humidity unless
- **protected by high-barrier** packaging.
- **Desiccant silica gel** in small packets, commonly included as protection against effects of moisture vapor.

- Drug substances that are subject to **oxidative degradation** may undergo a greater degree of degradation when packaged in plastic than in glass.

- Liquid in plastic may **lose drug molecules** or solvent to the container, altering the concentration of drug in product and affecting its potency.

 Leaching is term used to describe **movement of components of container to contents**.

 Compounds leached: polymer additives, such as the plasticizers, stabilizers, or antioxidants.

 The leaching occurs when liquids or semisolids are packaged in plastic. Little leaching occurs when tablets or capsules are packaged in plastic.

 influenced **by temperature**, **excessive agitation** of the filled container, and the **solubilizing effect of liquid contents** on one or more of the polymer additives