PHARMACEUTICAL CONTAINERS AND CLOSURES: AN OVERVIEW

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INTRODUCTION

- *Packaging is the process by which the pharmaceuticals are suitably placed so that they should retain their therapeutic effectiveness from the time of their packaging till they are consumed.*
- ***Definition:***

  "Packing is the art and science which involves preparing the articles for transport, storage, display and use."
- *Pharmaceutical packaging is the means of providing protection, presentation, identification, information and convenience to encourage compliance with a course of therapy.*
- ***Composition of package:***

  (a) Container
  (b) Closure
  (c) Carton or Outer
  (d) Box

The ideal container or package should:

1. Protect the contents from the following environmental hazards:

- *Light - protect the contents from light*
- *Temperature - be capable of withstanding extremes of temperature.*
- *Moisture - be capable of withstanding extremes of humidity.*
- *Atmospheric gases - protect the contents from the effect of atmospheric gases (e.g. aerial oxidation).*
- *Particles - protect from particulate contamination.*
- *Microorganisms - protect from microbial contamination.*

2. Protects the content from the following mechanical hazards

- *Vibration - Usually due to transportation*
- *Compression - this usually includes pressure applied during stacking.*
- *Shock - such as impact, drops or rapid retardation.*
- *Puncture - penetration from sharp objects or during handling operations.*
- *Abrasion - this may create electrostatic effects.*

3. They must not add or permit loss to its contents:

- *Protect the contents from both loss and gain of water.*
- *Protect the contents from loss of volatile materials*
- *Must not shed particles into the contents.*
- *Must not leach anything to the contents.*

4. Must have a pharmaceutically elegant appearance:

- *In a competitive market the appearance of a package first draws the attraction of the consumers than its contents.*
- *Must be easy to label and thus to identify the product.*

5. Must be convenient and easy to use by the patient.

6. Must be cheap and economical.

7. Must not react with the content.

8. Must be biodegradable.

SELECTION OF PACKAGING MATERIAL

- *The materials selected for packaging must have the following characteristics:*
- *They must protect the preparation from environmental conditions.*
- *They must not be reactive with the product,*
- *They must not impart tastes or odors to the products,*
- *They must be non-toxic,*
- *They must be FDA (Food & Drug Administration) approved,*
- *They must meet applicable tamper-resistance requirements*
- *They must be adaptable to commonly employed high-speed packaging equipment. and*
- *They must have reasonable cost in relation to the cost of the product.*

Categorically differentiating pharmaceutical packaging:

- ***Primary Packaging:*** *This is the first packaging envelope which is in touch with the dosage form or equipment (i.e. bottle, cap, cap liner, label etc). The packaging needs to be such that there is no interaction with the drug and will provide proper containment of pharmaceuticals.*
  E.g. Blister packages, Strip packages, etc.

- *The main functions of the primary package are to contain and to restrict any chemical, climatic or biological or occasionally mechanical hazards that may cause or lead to product deterioration. Packaging must also function as a means of drug administrations.*

- ***Secondary Packaging:*** *This is consecutive covering or package which stores pharmaceuticals packages in it for their grouping.*

E.g. Cartons, boxes, etc. OR

- *The packaging external to the primary package is known as the secondary packaging.*
- *The secondary packaging mainly provides the additional physical protection necessary to endure the safe warehousing and for refill packaging.*

- ***Tertiary packaging:*** *This is to provide bulk handling and shipping of pharmaceuticals from one place to another.*

E.g. Containers, barrels, etc.

Types of primary and secondary packaging material		
Material	Type	Example of use
Glass	Primary	Metric medical bottle, ampoule, vial
Plastic	Primary	Ampoule, vial, infusion fluid container, dropper bottle
	Secondary	Wrapper to contain primary pack
Cardboard	Secondary	Box to contain primary pack
Paper	Secondary	Labels, patient information leaflet

- *Apart from primary and secondary packaging, two types of special packaging are currently in use, as follows:*

- • ***Unit-dose packaging***. *This packaging guarantees safer medication by reducing medication errors; it is also more practical for the patient. It may be very useful in improving compliance with treatment and may also be useful for less stable products.*

- • ***"Device" packaging.*** *Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration by means of devices such as prefilled syringes, droppers, transdermal delivery systems, pumps and aerosol sprays. Such devices ensure that the medicinal product is administered correctly and in the right amount.*

CONTAINER:

- *A container for a pharmacopoeial article is intended to contain a drug substance or drug product with which it is, or may be in direct contact. The closure is a part of the container.*

QUALITIES OF GOOD CONTAINER:

- *The container must be neutral towards the material which is stored in it.*
- *The container must not interact physically or chemically with the substance which it holds.*
- *It should help in maintaining the stability of product against the environmental factors which causes its deterioration.*
- *It should be made of materials which can withstand wear and tear during normal handling.*
- *It should be made of materials which can withstand wear and tear during normal handling.*
- *It should be able to withstand changes in pressure and temperature.*
- *The materials used for making of the container must be non-toxic.*

TYPES OF CONTAINERS:

Containers are divided into following types on the basis of their utility:

Well – closed containers: *A well-closed container protects the contents from loss during transportation, handling, storage or sale.*

Single dose containers : *These containers are used to supply only one of medicament and hold generally parenteral products.*

E.g. ampoules and vials

❖***Multi dose containers:*** *These containers allow the withdrawal of dose at various intervals without changing the strength, quality or purity of remaining portion. these containers hold more than one dose and are used for injectables. E.g. vials*

❖***Light-resistant containers:*** *These containers protect the medicament from harmful effects of light. These containers are used to store those medicaments which are photo-sensitive.*

❖***Air-tight containers:*** *These are also called hermetic containers. These containers have air-tight sealing or closing. These containers protect the products from dust, moisture and air. Where as air-tight sealed containers are used for injectables, air-tight closed containers are meant for the storage of other products.*

❖***Aerosol containers:*** *These containers are used to hold aerosol products. These containers have adequate mechanical strength in order to bear the pressure of aerosol packing.*

FACTORS INFLUENCING THE CHOICE OF PACKAGE:

- ***The product:***

  The physical and chemical characteristics of the drug entity, the excipients, the formulation, route of deterioration of the product, type of patient (baby, child, teenager, adult, elderly, infants etc) must be considered while dealing with the pharmaceutical product. Apart from the properties of drug, package style to attract patient and other legal requirements should also be considered during selection.

- ***The market:***

  The channel of sale should be considered, i.e. where, when, how and by whom it is to be used or administered (e.g. doctor, dentist, nurse, patients etc), whether for home trade and/ or export. The quantity per package and follow up sale must all be carefully considered during package design and selection.

- ***The distribution system:***

  The distribution system should be carefully monitored, e.g. conventional wholesale/ retail outlet or direct or selective outlets. Less sophisticated transport systems like mules, donkeys, camels etc requires additional protection if intermediate storage facilities are non existent.

- ***Manufacturing facilities:***

  The stability of the manufacturing facilities should be considered due to new package, increased sale, improvements in Good Manufacturing Practice, revised product, new product etc.

PACKAGING MATERIALS

The following materials are used for the construction of containers and closures

1. Glass: *- (i) Type-I Borosilicate glass*

(ii)Type-II Treated sodalime glass

(iii)Type-III Regular soda-lime glass

(iv)Type-NP General purpose soda lime glass

(v)Coloured glass

2. Metals: *(i) Tin (ii) Iron (iii) Aluminium (iv) Lead.*

3. Plastics*: (a) Thermosetting resins:* *(i) Phenolics (ii) Urea*

(b) Thermoplastic resins: *(i)Polyethylene*

(ii)Polypropylene *(iii)Polyvinylchloride (PVC)*

(iv) Polystyrene *(v)Polycarbonate*

(vi)Polyamide (Nylon) *(vii)Polyethylene terephthalate (PET)*

4. Rubber*: (i) Natural rubber (ii)Neoprene rubber (iii)Butyl rubber.*

GLASS CONTAINERS:

Glass is the preferred packaging material.

COMPOSITION OF GLASS

- *Sand (silicon dioxide) Soda ash (sodium carbonate) Limestone (calcium carbonate) Cullet (broken glass) - aluminium, boron, potassium, magnesium, zinc, barium,*
- *Amber: light yellowish to deep reddish brown, carbon and sulphur or iron and manganese dioxide*
- *Yellow: Compounds of cadmium and sulphur*
- *Blue: Various shades of blue, cobalt oxide or occasionally copper (cupric) oxide*
- *Green: iron oxide, manganese dioxide and chromium dioxide*

MANUFACTURE OF GLASS:

The four basic processes used in the production of glass are:

- ***Blowing*** *uses compressed air form the molten glass in the cavity of metal mold.*
- *In* ***drawing*** *, molten glass is pulled through dies or rollers that shape the soft glass.*
- *In* ***pressing*** *mechanical force is used to press the molten glass against the side of a mold.*
- ***Casting*** *uses gravity or centrifugal force to cause molten glass to form in the cavity of mold.*

ADVANTAGES

- *They are hygienic and suitable for sterilization*
- *They are relatively non reactive (depending on the grade chosen)*
- *It can accept a variety of closures*
- *They can be used on high speed packaging lines*
- *They are transparent.*
- *They have good protection power.*
- *They can be easily labeled.*

DISADVANTAGES

- *It is relatively heavy*
- *Glass is fragile so easily broken.*
- *Release alkali to aqueous preparation*

Type I glass:

Composition: *Neutral glass, borosilicate glass (silica (silicon dioxide, SiO_2) and boron oxide).*

Advantages:

- *It possesses a high hydrolytic resistance.*
- *It is the most inert type of pharmaceutical glass.*
- *It has the lowest coefficient of thermal expansion (and hence suitable for sterilization by heat…..for ampoules and vials).*

Disadvantages:

- *It has very high glass transition temperature so needs complicated processing.*
- *And therefore expensive.*

Uses:

- *Type I glass is suitable for packing all pharmaceutical preparations.*
- *It is widely used as glass ampoules and vials to package fluids for injection.*
- *In contrast to the other types of glass (type II and III), this type has no/little amounts of basic oxides, so It is used to package solutions that could dissolve basic oxides in the glass.*

Type II glass

Composition: *soda-lime-silica glass.*

Soda (Na_2CO_3) is used to decrease the glass transition temperature of silica. However, soda would increase water solubility of silica, so lime (CaO) is used to increase the hydrolytic resistance. This type would also contain other oxides.

Advantages*:*

- *This glass has a lower melting point than Type I glass. It is thus easier to produce and consequently cheaper.*
- *High hydrolytic resistance due to surface treatment of the glass.*

Uses:

- *Type II glass used to package aqueous preparations.*
- *However, as it contains basic oxides, it is not used to package parenteral formulations with a pH <7 (i.e. acidic); this would increase the pH of the formulation and could affect the drug stability and potency.*
- *It is the glass used to produce containers for eye preparations and other dropper bottles.*

Type-III regular soda lime glass

- *Containers are untreated are made of commercial soda lime glass of average are better than average chemical resistance.*
- *It contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances.*
- *Flakes separate easily.*

- ***Uses:***

- *For all solid dosage forms.*
- *For oily injections.*

Type NP-general purpose soda lime glass

- *Containers are made of soda lime glass supplied for non parental products, intended for oral or topical use.*

- ***Uses:***

- *For oral use.*
- *Topical purpose.*

PLASTICS

According to British standards institutes plastics represents;

" A wide range of solid composite materials which are largely organic, usually based upon synthetic resins or upon modified polymers of natural origin and possessing appreciable mechanical strength. At a suitable stage in their manufacturing, most plastics can be cast, molded or polymerized directly into shape".

- ***Classes of plastics:***

There are two classes of plastics, reflecting the behavior with respect to individual or repeated exposure to heating and cooling.

- ***Thermoplastics***

- *Capable of being shaped after initial heating and solidifying by cooling.*
- *Resistant to breakage and cheap to produce and providing the right plastics are chosen will provide the necessary protection of the product in an attractive containers.*
- *E.g. Polystyrene, polyethylene and polyvinyl chloride.*

- *Thermosets*

- *They need heat for processing into a permanent shape. During heating such materials form permanent crosslinks between the linear chains, resulting in solidification and loss of plastic flow.*
- *E.g. Phenolic, urea and melamine are representative of thermosets.*

USES

Used for many types of pack including; rigid bottles for tablets and capsules, squeezable bottles for eye drops and nasal sprays, jars, flexible tubes and strip and blister packs.

ADVANTAGES

- *Least expensive than glasses*
- *Ease of transportation*
- *No risk of breakage*
- *Flexible*
- *Light in weight*

DISADVANTAGES

- *They are not as chemically inert as Type -I glass.*
- *They are not as impermeable to gas and vapour as glass.*
- *They may possess an electrostatic charge which will attract particles.*

TYPES OF PLASTICS

- ***POLYETHYLENE***

- *This is used as high and low density polyethylene*
- *Low density polyethylene (LDPE) is preferred plastic for squeeze bottles.*

Properties: Ease of processing , barrier to moisture, strength /toughness, flexibility, ease of sealing.

- *High density poly ethylene (HDPE) is less permeable to gases and more resistant to oils, chemicals and solvents.*

Properties: Stiffness, strength / toughness, resistance to chemicals.

It is widely used in bottles for solid dosage forms.

Drawback: prone to stress cracking in the presence of surfactants or vegetable or mineral oils.

- ***POLYPROPYLENE***

- *It has good resistance to cracking when flexed.*
- *Good resistance to heat sterilization.*
- *It is colorless, odorless thermoplastic material with excellent tensile properties even at high temperature.*
- *Excellent resistance to strong acids and alkalis.*
- *Low permeability to water vapour*
- *Permeability to gases is intermediate between polyethylene HD and un-plasticized PVC*
- *Suitable for use in closures , tablet containers and intravenous bottles.*

- ***POLYSTYRENE***

- *Versatility, insulation, clarity, easily foamed ("Styrofoam").*
- *It is also used for jars for ointments and creams with low water content.*
- *Drawback: Chemicals like isopropyl myristate produce crazing(a fine network of surface cracks) followed by weakening and eventually collapsible of the container.*

POLYVINYL CHLORIDE

- *Versatility , ease of blending, strength / toughness, resistance to grease/oil, resistance to chemicals, clarity.*
- *Used as rigid packaging material and main component of intravenous bags.*
- *Drawback: Poor impact resistance which can be improved by adding elastomers to the plastics but it will increase its permeability.*

POLY VINYLEDENE CHLORIDE:

- *Excellent barrier properties against: moisture, water vapour, UV light, aroma, inorganic acids, alkalies, aqueous salt solutions, organic water soluble acids, aliphatic hydrocarbons , esters of long chain fatty acids, detergent base materials, emulsifying agents and wetting agents.*
- *Good thermoform ability.*
- *PVDC is very cost-effective, as coating weight can be customized depending on the requirements of the barrier properties.*
- *Medical grade and non-toxic.*
- *High levels of transparency which improves the aesthetics of the product.*

DRUG-PLASTIC CONSIDERATIONS

- *A packaging system must protect the drug without altering the composition of the product until the last dose is removed.*
- *Drug-plastic considerations have been divided into five categories:*

1. *Permeation*
2. *Leaching*
3. *Sorption*
4. *Chemical reaction*
5. *Alteration*

Permeation:

- *It is the transmission of gases, vapors or liquids through plastic packaging material.*
- *Permeation of water vapor and oxygen through plastic wall into the drug is a major problem is the dosage form is sensitive to hydrolysis and oxidation.*
- *The volatile ingredients might change when stored in plastic containers and the taste of the medicinal products may change for the same reason of permeation.*

Leaching:

- *Some plastic containers have one or more ingredients added to stabilize it, these may leach into the drug product.*
- *Problems may arise with plastics when coloring agents are added in small quantities to the formula.*
- *Particular dyes may migrate into the parental solution and cause a toxic effect.*

- ***Sorption:***

- *This process involves the removable of constituents from the drug product by the packaging material.*
- *The therapeutic efficacy of the product may be reduced due to sorption.*
- *Sorption may change the chemical structure, pH, solvent system, concentration of active ingredients and temperature etc…*

- ***Chemical reactivity:***

- *Certain ingredients in plastic formulations may react chemically with one or more components of the drug product.*
- *Even in micro quantities if incompatibility occurs may alter the appearance of the plastic or the drug product.*

- ***Modification:***

- *The physical and chemical alteration of the packaging material by the drug product is called modification.*
- *Some solvent systems found to be considerable changes in the mechanical properties of the plastics.*
- *For example oils have a softening effect on polyethylene, hydrocarbons attack polyethylene and PVC.*

METALS

- *Metal containers are used solely for medicinal products for non-parenteral administration.*
- *Metal is strong, opaque, impermeable to moisture, gases, odors, light, bacteria, and shatterproof, it is the ideal packaging material for pressurized containers.*
- *It is resistant to high and low temperatures*
- *They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders.*
- *Aluminium and stainless steel are the metals of choice for both primary and secondary packaging for medicinal products.*
- *Form an excellent tamper evident containers.*

ALUMINIUM

- *It is relatively light yet strong*
- *Barrier to light and chemicals*
- *Impermeable and easy to work into a variety of formats, depending on its thickness.*
- *Thickest aluminium is used for rigid containers such as aerosol cans and tubes for effervescent tablets.*
- *Intermediate thickness are when mechanical integrity is still important but the pack should be capable of being reformed under a reasonable force.*

  e.g. Collapsible tubes for semi solid preparations or roll on screw caps.
- *Thinnest aluminium is used in flexible foil that are usually a component of laminated packaging material.*

- ***Disadvantages and their overcome solution***

- *Major disadvantage is its reactivity in raw state, although it rapidly forms a protective film of aluminium oxide it is still liable to corrosion (when exposed to some liquids and semi solid formulations, particularly at extreme pH or if the product contains electrolytes.*

- *To overcome this problem, Aluminium is lined with epoxide, vinyl or phenolic*

- *resins.*

- *They are work hardening like collapsible tubes are made by impact extrusion which tends to make aluminium less flexible.*

- *To overcome, flexibility has to restored by an annealing stage.*

- ***TIN***
- ***Advantages:***

- *This metal is very resistant to chemical attack.*
- *Readily coats a number of the metals e.g. tin-coated lead tubes combine the softness of lead with the inertness of tin and for this reason it was formerly used for packaging fluoride toothpaste.*

- ***Disadvantages:***

Tin is the most expensive metal among tin, lead, aluminium and iron.

- ***Uses:***

- *Tin containers are preferred for foods, like milk powder containers are coated with tin.*
- *Currently, some eye ointment still packaged in pure tin ointment tubes.*

- ***IRON***
- ***Advantages:***

  Iron as such is not used for pharmaceutical packaging, large qualities of tin-coated steel, popularly called 'tin', combines the strength of steel with the corrosion resistance of tin.

- ***Disadvantages:***

  If an aqueous liquid can penetrate a pinhole or other fault in the layer of tin, which is virtually a short-circuited galvanic cell is set up and the intense chemical reaction which results brings about rapid corrosion of underlying steel. As a further measure the tin surface is lacquered.

- ***Uses:***

  Fabrication of milk containers, screw caps and aerosol cans.

- ***LEAD***
- ***Advantages:***

- *Lowest cost of all the metals used in pharmaceutical containers.*
- *Soft metal.*

- ***Disadvantages:***

Lead when taken internally there is risk of lead poisoning. So lead containers and tubes should always have internal lining of inert metal or polymer.

- ***Uses:***

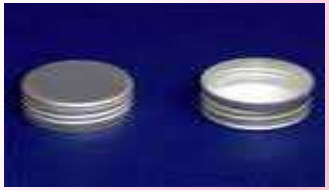
With lining lead tubes are used for such product as fluoride tooth paste.

CLOSURES:

- *A closure is the part of the package which prevent the contents from escaping and allow no substance to enter the container.*

- *Closures are available in five basic designs:*

1. *Screw on, threaded or lug*
2. *Crimp on(crowns)*
3. *Press on(snap)*
4. *Roll on and*
5. *Friction*



- ***Threaded screw cap:***

- *When a screw cap is applied, its threads engaged with the corresponding threads molded on the neck of the bottle.*
- *A liner in the cap, pressed against the opening of the container, seals the product in the container and provide the resistance to chemical and physical reaction with the product.*
- *The screw cap is commonly made of metal or plastics. The metal is usually tin plate or aluminum and in plastic is thermoplastic and thermosetting material.*

Lug cap:

- *The lug cap is similar to the threaded screw cap and operates on the same principle.*
- *It is simply an interrupted thread on the glass finish, instead of a continuous thread.*
- *Unlike the threaded closure, it requires only a quarter turn.*
- *The lug cap is used for both normal atmosphere pressure and vacuum pressure closing.*

- ***Crown caps:***
  - *This style cap is commonly used as a crimped closure for beverage bottles.*

- ***Roll-on closures***
  - *The aluminum roll on cap can be seal securely, opened easily and resealed effectively.*
  - *Resealable, non resealable and pilfer proof types of roll on closures are available for use on glass or plastic bottles.*

- ***Pilfer proof closures***

- *It is similar to roll on closure but has a greater skirt length.*
- *This additional length extends below the threaded portion and fastened to the basic cap by the series of narrow bridges.*
- *When the closure is removed the extra portion remains in the space on neck of the container, this indicates that the package has been opened.*

- ***CLOSURE LINERS:***
- *A liner may be defined as any material that inserted in a cap to effect a seal between the closure and the container.*
- *It is of two types:*

1. ***Homogeneous liner***

- *These are one piece liners available as disk or a ring of rubber or plastic.*
- *It can be withstand high temperature sterilization.*

2. ***Heterogeneous liners***

- *These are composed of layers of different materials chosen for specific requirements.*
- *It consists of facing and backing. Facing is in contact with product and backing provides questioning effect.*

Factors in selecting a liner:

- *Chemical inertness – should be chemically inert*
- *Appearance, thickness etc.*
- *Gas and water-vapour transmission rates – should be low.*
- *Torque require to remove the cap – should be optimum.*
- *heat resistance – e.g. during autoclaving should be thermostable.*
- *Shelf-life – should not change their shape during storage.*
- *Economics – should be cheap.*

RUBBERS (Elastomers):

- *Excellent material for forming seals, used to form closures such as bungs for vials or in similar applications such as gaskets in aerosol cans.*

- ***Categories of Rubbers:***

1) ***Natural rubbers;***

- *Suitable for multiple use closures for injectable products as rubber reseals after multiple insertion of needle.*
- *Disadvantages are;*
  - *i. It doesn't well tolerate multiple autoclaving becoming brittle and leads to relative degree of extractable material in presence of additives.*
  - *ii. Risk of product absorbing on or in to a rubber.*
  - *iii. It has certain degree of moisture & gas permeation.*

*2) **Synthetic rubber:***

- *Have fewer additives and thus fewer extractable and tends to experience less sorption of product ingredients.*
- *Are less suitable for repeated insertions of needle because they tend to fragment or core pushing small particles of the rubber in to the product.*
- *E.g. Silicone, butyl, bromobutyl, chlorobutyl etc.*
- *Silicone is least reactive but it does experience permeability to moisture and gas.*
- *Softer rubbers experience less coring and reseal better, harder rubbers are easier to process on high speed packaging lines.*

TYPES OF RUBBER

1. BUTYL RUBBER

These are copolymers of isobutylene with 1-3% of isoprene or butadiene.

- ***Advantages:-***

- *After vulcanization butyl rubber possesses virtually no double bond, consequently they are most resistant to aging and chemical attack.*
- *Permeability to water vapour and air is very low.*
- *Water absorption is very low.*
- *They are relatively cheaper compared to other synthetic rubbers.*

- ***Disadvantages***

- *Slow decomposition takes place above 130^0C.*
- *Oil and solvent resistance is not very good.*

2. NITRILE RUBBER

- ***Advantages:***

- *Oil resistant due to polar nitrile group.*
- *Heat resistant.*

- ***Disadvantage***

- *Absorption of bactericide and leaching of extractives are considerable.*

3. CHLOROPRENE RUBBERS (NEOPRENE)

These are polymers of 1:4 chloprene.

- **Advantages**

- *Due to the presence of –Cl group close to the double bond so the bond is resistant to oxidation hence these rubbers age well.*
- *This rubber is more polar hence oil resistant.*
- *Heat stability is good (upto 150^0C).*
- *Water absorption and permeability are less than for natural rubbers.*

4. SILICONE RUBBERS

- **Advantages**

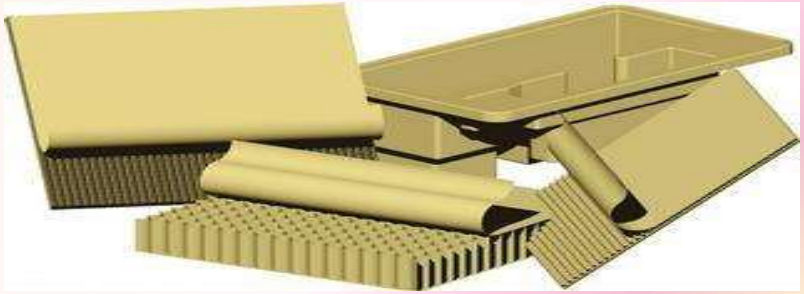
- *Heat resistance (upto 2500C).*
- *Extremely low absorption and permeability of water.*
- *Excellent aging characteristics due to their saturated chemical structures.*
- *Poor tensile strength.*

- **Disadvantages**

- *They are very expensive.*

FIBROUS MATERIAL

- *The fibrous materials are the important part of pharmaceutical packaging.*
- *Fibrous materials include: Papers, Labels, Cartons, Bags, Outers, Trays For Shrink Wraps, Layer Boards On Pallets, etc.*
- *The Applications as well as Advantages of Cartons include:*
  - ✓ *Increases display area*
  - ✓ *Provides better stacking for display of stock items*
  - ✓ *Assembles leaflets*
  - ✓ *Provides physical protection especially to items like metal collapsible tubes.*
  - ✓ *Fiberboard outers either as solid or corrugated board also find substantial application for bulk shipments.*
  - ✓ *Regenerated cellulose film, trade names Cellophane & Rayophane, is used for either individual cartons or to assemble a no. of cartons.*



FILMS FOILS AND LAMINATES

- *Regenerated cellulose film based on viscose (chemical used for manufacturing of rayon) & laminating two or more types of films, cellulose coatings, foil and paper play diff roles such as supportive, barrier, heat seal & decorative.*
- *For Example:*

  Aluminum foil even in the thinnest gauges offers the best barrier properties, which are not approached even by the most impermeable plastics.
- ***"Metallization":*** *A relatively new process whereby particles of metal are laid down onto a surface under vacuum, can significantly improve the barrier properties of a material but these do not approach the properties of a pure foil.*
- *In the newer technology "Co-Extrusion", a number of plastic plies are extruded in combination to produce cheaper laminations.*

- *Uses of films, foils, laminations:*
  - *Strip packs*
  - *Blister packs*
  - *Sachets*
  - *Diaphragm seals for bottles*
  - *Liners for boxes either attached or loose bag-in-box systems & bags.*

- ***Foil blisters:***

  When sealed with a metal foil-cover, the blister can provide a hermetic pack i.e. an isolated system, which excludes any exchange of gases between the product & surrounding atmosphere.

- ***Alu-alu foil*** *is the best pharmaceutical packaging film for tablets, capsules, which is taking place of PVC film.*
  - *Applicable to tablets, capsules, pills, etc.*
  - *It's a good substitute for PVC sheet.*
  - *No cracking, delamination or pinholes*
  - *It has the quite good blocking properties effectively protecting drugs from water vapor, oxygen and ultraviolet.*
  - *It is particularly suitable for packing moisture-sensitive drugs or those sold in the hot and humid areas.*

TAMPER RESISTANT PACKAGING:

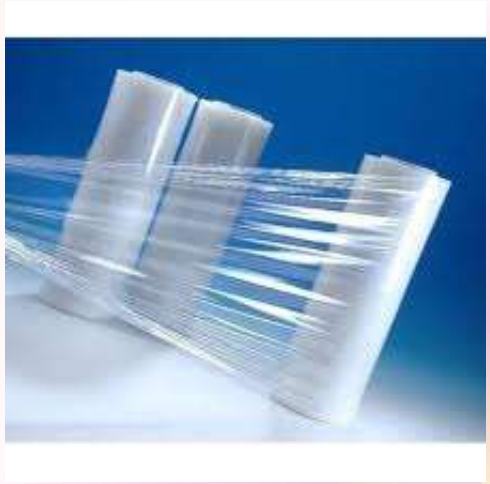
- *The requirement for tamper resistant packaging is now one of the major considerations in the development of packaging for pharmaceutical products.*
- *A tamper resistant package is provided with an indicator or barrier before entering the package, so that if this indicator or barrier is broken, the buyer immediately gets the evidence that the product has been opened or tampered.*
- *Especially over the counter products require tamper resistant packaging.*

- ***The following packages are approved by FDA as tamper resistant packaging systems:***

- ✓ *Film wrappers*
- ✓ *Blister package*
- ✓ *Strip package*
- ✓ *Bubble pack*
- ✓ *Shrink seals and bands*
- ✓ *Foils, paper or plastic pouches*
- ✓ *Bottle seals*
- ✓ *Tape seals*
- ✓ *Breakable caps*
- ✓ *Sealed tubes*
- ✓ *Aerosol containers*
- ✓ *Sealed cartons.*

Film wrappers

- *A transparent film with distinctive design is wrapped securely around the entire product container. The film must be cut or torn to remove the product. The wrapper must have an identifying characteristic (e.g. a pattern, name, registered trade mark, logo, or picture) that cannot be readily duplicated. Tinted wrappers are not acceptable as an identifying characteristic because of the possibility that their material may be available to the public. A reasonably tight "fit" of the film around the container must be achieved, e.g. by a heat shrink type process.*
- *Sealing of a film wrapper with overlapping end flaps is acceptable only if the ends cannot be opened and resealed without leaving visible evidence of tampering. The use of cellophane with overlapping end flaps is not acceptable because of the possibility that the ends can be opened and resealed without leaving visible evidence that tampering has occurred.*



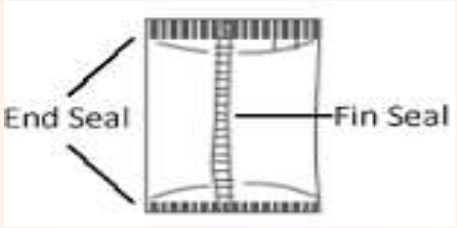
- *Although film can be accomplished in several ways and varies in configuration from packaging equipment to packaging equipment, it can be generally categorized in to following types:*

- *Fin seal wrapper*
- *End-folded wrapper*
- *Shrink wrapper*

- ***Fin seal wrapper:***

These seals are formed by crimping the film together and sealing together the two inside surfaces of the film, producing a "fin" seal. The overwrap can be removed or opened only by tearing the wrapper.

Materials: Polyethylene or Surlyn (Du Pont's Ionomer resin)



- ***End-folded wrapper:*** *This wrapper is formed by pushing the product in to sheet of overlapping film, which forms the film around the product and fold the edges in gift wrap fashion. Film used must be heat-sealable on both surfaces. To be tamper-resistant, the overwrap must be well sealed must be printed or uniquely decorated to exclude the possibility of having an alternate overwrap substituted in its place. The printed surface of the carton being wrapped may also be coated with heat sensitive varnish, which causes overwrap to bond permanently to the paperboard carton during sealing of overwrap. The removal of the overwrap would deface the carton, making the carton unsuitable for reuse.*

Materials:

- *Cellophane coated in both side by heat sealable polyvinylidene chloride (PDVC) or nitrocellulose-PDVC provides durable moisture barrier.*
- *Polypropylene coated with heat sealable acrylic coating or polypropylene is added with heat sealable modifiers.*

- ***Shrink wrapper:*** *The shrink wrap concept involves the packaging of a product in thermoplastic film that has been stretched and oriented during its manufacture and that has the property of reverting back to its unstretched dimensions as the film unwinds on the overwrapping machine, a pocket is formed in the fold of the sheet, in to which the product is inserted. An L shaped sealer seals the remainder of overwrap and trims off the excess film. The loosely wrapped product is then moved through heated tunnel which shrinks the overwrap in to a tightly wrapped unit.*

Materials: Heat shrinkable grades of polypropylene, polyethylene and polyvinylchloride (PVC).

❖ ***Blister or strip packs:***

- *It is a packaging configuration capable of providing excellent environmental protection, coupled with an esthetically pleasing an efficacious appearance .it also provides user functionality in terms of convenience, child resistance, and now temper resistance.*
- *The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum drawing the softened sheet of plastic in to a contoured mold. After cooling, the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with product and lidded with a heat-sealable backing material. The backing material, or lidding, can be of either a push through or peelable type.*
- *Dosage units (for example, capsules or tablets) are individually sealed in plastic or foil. The individual compartment must be torn or broken to obtain the product. The backing materials cannot be readily separated from the blisters or easily replaced without leaving evidence of tampering.*

Strip package

- *A strip package is a form of unit dose packaging of tablet or capsules. A strip package is formed by feeding two webs of heat sealable flexible film through either a heated crimping roller or a heated reciprocating platen. The product is dropped into the pocket formed prior to forming the final set of seals. Since the sealing is usually accomplished between pressure rollers, a high degree of seal integrity is possible.*

❖ ***Bubble packs***

- *The bubble pack can be made in several ways but is usually formed by sandwiching the product between a thermoformable, extensible, or heat-shrinkable plastic film and a rigid backing material, this is passed through a heated tunnel, which shrinks the film into bubble or skin over the product, firmly attaching it to the backing card.*
- *The product and container are sealed in plastic and mounted in or on a display card. The plastic must be torn or broken to remove the product. The backing material cannot be readily separated from the bubble or easily replaced without leaving evidence of tampering*

Heat shrink bands or wrappers

- *The shrink band concept makes use of the heat-shrinking characteristic of a stretch oriented polymer usually PVC. The polymer is manufactured as an extruded, oriented tube in a diameter slightly larger than the cap and neck ring of the bottle to be sealed. Bands or wrappers with a distinctive design (e.g., a pattern, name, registered trade mark, logo, or picture) are shrunk by heat to seal the union of the cap and container. The seal must be cut or torn to remove the product.*
- *The band or wrapper cannot easily be worked off and reapplied without visible damage to the band. Use of a perforated tear strip can enhance tamper evidence. Cellulose wet shrink seals are not acceptable as the knowledge of how to remove and reapply these seals without evidence of tampering is widespread.*

Foil, paper, or plastic pouches

- *The flexible pouch is packaging concept capable of providing not only a package that is tamper resistant, but also, by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, sealing (f/f/s) equipment.*
- *The product is enclosed in an individual pouch that must be torn or broken to obtain the product. The pouch should have a distinctive design (e.g., a pattern, name, registered trademark, logo, or picture).The end seals of the pouches cannot be separated and resealed without showing visible evidence of entry.*

❖ ***Bottle mouth inner seals***

- *A bottle may be made tamper-resistant by bonding an inner seal to the rim of the bottle in such a way that access to the product can only be attained by irreparable destroying the seal.*
- *Various inner seal compositions may be used like:*

- *Glassine and foil laminations.*
- *Glue mounted.*
- *Pressure sensitive adhesive.*
- *Heat sensitive adhesive.*

- *Paper, thermal plastic, polystyrene foam (except those applied with pressure sensitive adhesive), plastic film, foil, or combinations thereof, with a distinctive design (e.g., a pattern, name, registered trademark, logo or picture) is sealed to the mouth of a container under the cap. The seal must be torn or broken to open the container and remove the product. Seals applied by heat induction to containers appear to offer a higher degree of tamper evidence than those that depend on an adhesive to create the bond.*
- *To meet tamper-resistant criteria, the inner seal must be printed or decorated with unique design. The seal must also be bonded sufficiently to ensure that its removal would result in destruction of the seal.*

❖ ***Tape seals***

- *Tape involves the application of a glued or pressure sensitive tape or label around or over the closure of the package, which must be destroyed to gain access to the packaged product. The paper used most often is high density lightweight papers with poor tear strength.*
- *Paper or foil with a distinctive design is sealed over all carton flaps or a bottle cap. The seal must be torn or broken to remove the product Tape seals are acceptable only if they contain a unique feature that makes it apparent if the seals have been removed and reapplied, e.g., a permanent adhesive.*

Breakable caps

- *Breakable closures come in many different designs. The roll on cap design used in the past for carbonated beverages uses an aluminum sheet, which placed over bottle neck during capping operation. The cap blank is held on the bottle under pressure while rollers crimp and contour the bottle tread into the cap blank. The bottom portion of cap is rolled around and under the locking ring on the bottle neck finish. This lower portion of the cap blank is usually perforated so that it breaks away when the cap is unscrewed, which serves as visible sign of prior opening.*
- *A ratchet-style plastic cap is also commonly used for a number of different products. In this design the bottom portion of closure has a tear-away strip, which engages a ratchet on the bottle neck. To remove the closure, the bottom portion of the closure must be torn away to disengage the ratchet and allow the removal of the cap.*

- ***Sealed metal tubes or plastic blind-end heat sealed tubes***

- *Collapsible tubes used for packaging are constructed of metal, plastic, or lamination of foil, paper, and plastic. Metal tubes are still used for those products that require high degree of barrier protection afforded by metal. Puncture inserts, which are usually made of aluminum 3 to 5 mil thick, are used to seal the tube opening for tamper resistance.*

- *Both ends of the tube are sealed. The mouth or blind-end must be punctured to obtain the product. A tube with a crimped end is acceptable if the crimped end cannot be breached by unfolding and refolding without showing visible evidence of tampering. Direct printing of the label on the container is preferred to using a label that could be removed and substituted.*

Cardboard cartons

- *Folding paperboard cartons have been used as secondary package for OTC products for many years. Seal end cartons uses externally applied glue or hot melt to provide carton sealing.*
- *Cardboard Cartons specifically designed to ensure that in order to obtain the product, the carton seal must be cut or must be non-resealable without showing visible evidence of en torn to remove the product and must not be able to be easily worked open and resealed without obvious damage to the carton.*

Aerosol containers

- *The aerosol container used for pharmaceutical products is usually made of drawn aluminium. The inside of the container can be specially coated if product compatibility is a problem.*
- *A hydrocarbon propellant in its cooled liquid phase is added to the container along with the product, and a spray nozzle contained in a gasketed metal ferrule is crimped over the opening of the aerosol container. A length of polyethylene tube, called a dip-tube, is attached to the inside of the spray nozzle and dips into the product, drawing product into the spray nozzle when the sprayer is activated.*
- *The spray nozzles are usually metered to allow a specific dose to be dispersed with each spray.*

QUALITY CONTROL TESTS FOR GLASSES

1) **CHEMICAL RESISTANT OF GLASS CONTAINERS**

A) POWDERED GLASS TEST: *It is done to estimate the amount of alkali leached from the powdered glass which usually happens at the elevated temperatures. When the glass is powdered, leaching of alkali is enhanced, which can be titrated with 0.02N sulphuric acid using methyl red as an indicator*

- ***Step-1*: Preparation of glass specimen**: *Few containers are rinsed thoroughly with purified water and dried with stream of clean air. Grind the containers in a mortar to a fine powder and pass through sieve no.20 and 50.*
- ***Step-2*: Washing the specimen**: *10gm of the above specimen is taken into 250 ml conical flask and wash it with 30 ml acetone. Repeat the washing, decant the acetone and dried after which it is used within 48hr.*
- **Procedure:**

  10gm sample is added with 50ml of high purity water in a 250ml flask. Place it in an autoclave at 121^{o}C±2^{o}C for 30min.Cool it under running water. Decant the solution into another flask, wash again with 15ml high purity water and again decant. Titrate immediately with 0.02N sulphuric acid using methyl red as an indicator and record the volume.

PREPARATION OF SPECIMEN FOR POWDERED

Preparation of specimen for powdered glass test:

Rinse 6 or more containers and dry them

↓

Crushed in to fragments

↓

Divide 100gms of coarsely crushed glass in to three equal parts

↓

Place 1 portion in a mortar

↓

Crush further by striking 3 or 4 blows with hammer

↓

Empty the mortar in to sieve 20

↓

Shake the sieves and remove the glass particles from # 20 and 40

↓

Crush them again and sieve them

↓

Transfer the retained portion on # 50

↓

Spread the specimen on a glazed paper and remove iron particles with the help of magnet

↓

Wash with 6 portions of 30ml acetone

↓

Dry the contents for 20mins at 140°c

↓

Transfer to weighing bottle and cool in a dessicator

↓

Final specimen should be used in powdered glass test

POWDERED GLASS TEST (According to USP volume 27)

Transfer 10gms of prepared specimen in a 250ml conical flask digested previously with high purity water in a bath at 90° c

↓

Add to conical flask containing 50ml high purity water

↓

Cap all the flasks and auto clave
Adjust temperature to 150°c

↓

Cold the temperature to 121°c for 30mins

↓

Cool the flasks under running water

↓

Wash the residue powdered glass (4 times with 15ml purity water)

↓

Add the decanted washings to main portion.

↓

Add five drops of methyl red solution.

↓

Titrate immediately with 0.02N sulfuric acid.

↓

Record the volume of 0.02N sulfuric acid.

↓

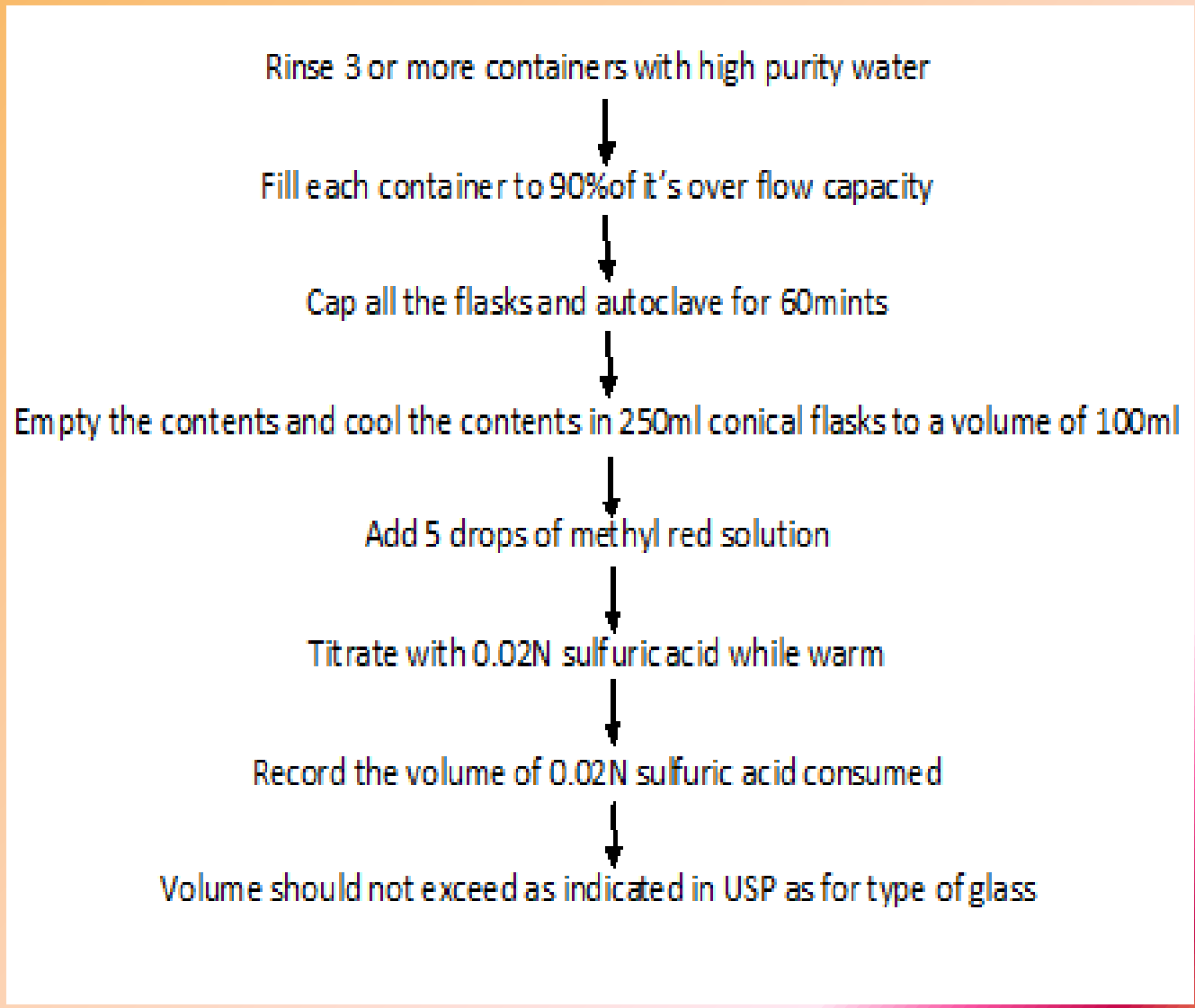
Volume does not exceed i.e. indicated in the USP as per the type of glass concerned

B) WATER ATTACK TEST:

- *This is only for treated soda lime glass containers under the controlled humidity conditions which neutralize the surface alkali and glass will become chemically more resistant.*
- ***Principle** involved is whether the alkali leached or not from the surface of the container.*
- ***Procedure:** Rinse thoroughly with high purity water. Fill each container to 90%of its overflow capacity with water and is autoclaved at 121^{o}C for 30min then it is cooled and the liquid is decanted which is titrated with 0.02N sulphuric acid using methyl red as an indicator. The volume of sulfuric acid consumed is the measure of the amount of alkaline oxides present in the glass containers.*

TESTS	CONTAINER	VOL.OF 0.02N H2SO4
Powdered glass test	Type I Type II Type III	1.0 8.5 15.0
Water attack test	Type II(100ml or below) Type II(above 100ml)	0.07 0.02

WATER ATTACK TEST (USP)



2) HYDROLYTIC RESISTANCE OF GLASS CONTAINERS:

- *Rinse each container at least 3 times with CO_2 free water and fill with the same to their filling volume. Also fill & Cover the vials and bottles and keep in autoclave. Heat to 100^{o}C for 10min and allow the steam to issue from the vent cork. Rise the temp from 100^{o}C to 121^{o}C over 20min. Maintain the temp at 121^{o}C to 122^{o}C for 60min.Lower the temp from 121^{o}C to 100C over 40min venting to prevent vacuum.*
- *Remove the container from autoclave, cool and combine the liquids being examined. Measure the volume of test solution into a conical flask and titrate with 0.01M HCl using methyl red as an indicator. Perform blank with water and the difference between the titration represents the volume of HCl consumed by the test solution.*

Nominal capacity of container (ml)	Number of containers to be used	Volume of test solution to be used for titration (ml)
5 or less	at least 10	50.0
6 to 30	at least 5	50.0
More than 30	at least 3	100.0

capacity of container (corresponding to 90% average flow volume)(ml)	Volume of 0.01M HCL Type I or type II glass(ml)	Volume of 0.01M HCL Type III glass(ml)
Not more than 1	2.0	20.0
More than1 but NMT 4	1.8	17.6
More than2 but NMT 5	1.3	13.2
More than5 but NMT 10	1.0	10.2
More than 10 but NMT 20	0.80	8.1
More than20 but NMT 50	0.60	6.1
More than50 but NMT 100	0.50	4.8
More than 100 NMT 200	0.40	3.8
More than 200 but NMT 500	0.30	2.9

3) ***ARSENIC TEST:***

- *This test is for glass containers intended for aqueous parenterals. Wash the inner and outer surface of container with fresh distilled water for 5min.Prep test as described in the test for hydrolytic resistance for an adequate no. of samples to produce 50ml.pipette out 10ml solution from combined contents of all ampoules to the flask. Add 10ml of HNO3 to dryness on the water bath, dry the residue in an oven at 130^{o}C for 30min cool and add 10ml hydrogen molybdate reagent .Swirl to dissolve and heat under water bath and reflux for 25min. Cool to room temp and determine the absorbance at 840nm.Do the blank with 10ml hydrogen molybdate.*
- *The absorbance of the test solution should not exceed the absorbance obtained by repeating the determination using 0.1ml of arsenic standard solution (10ppm) in place of test soln.*

4) THERMAL SHOCK TEST:

- *Place the samples in upright position in a tray. Immerse the tray into a hot water for a given time and transfers to cold water bath, temp of both are closely controlled. Examine cracks or breaks before and after the test. The amount of thermal shock a bottle can withstand depends on its size, design and glass distribution. Small bottles withstand a temp differential of 60 to 80^{o}C and 1 pint bottle 30 to 40^{o}C. A typical test uses 45C temp difference between hot and cold water.*

5) INTERNAL BURSTING PRESSURE TEST:

- *The most common instrument used is American glass research increment pressure tester .The test bottle is filled with water and placed inside the test chamber. A scaling head is applied and the internal pressure automatically raised by a series of increments each of which is held for a set of time. The bottle can be checked to a preselected pressure level and the test continues until the container finally bursts.*

6) LEAKAGE TEST:

- *Drug filled container is placed in a container filled with coloured solution (due to the addition of dye)which is at high pressure compared to the pressure inside the glass container so that the coloured solution enters the container if any cracks or any breakage is present.*

7) ANNEALING TEST:

- *The sample is examined by polarized light in either a polariscope or strain viewer. The strain pattern is compared against standard discs or limit samples.*

8) VERTICAL LOAD TEST:

- *The bottle is placed between a fixed platform & a hydraulic ramp platform which is gradually raised so that a vertical load is applied. The load is registered on pressure gauge.*

9) AUTOCLAVING (121 °C for 60 min)

- *Ability of a filled or empty container to withstand autoclaving may be checked.*

QUALITY CONTROL TESTS FOR PLASTICS:

1) LEAKAGE TEST:

- *Fill 10 containers with water, fit with intended closures and keep them inverted at room temperature for 24hr.The test is said to be passed if there is no signs of leakage from any container.*

Leakage test for plastic containers (non-injectables & injectables 1996 IP):

Fill 10 plastic containers with water and fit the closure

↓

Keep them inverted at room temperature for 24 hrs

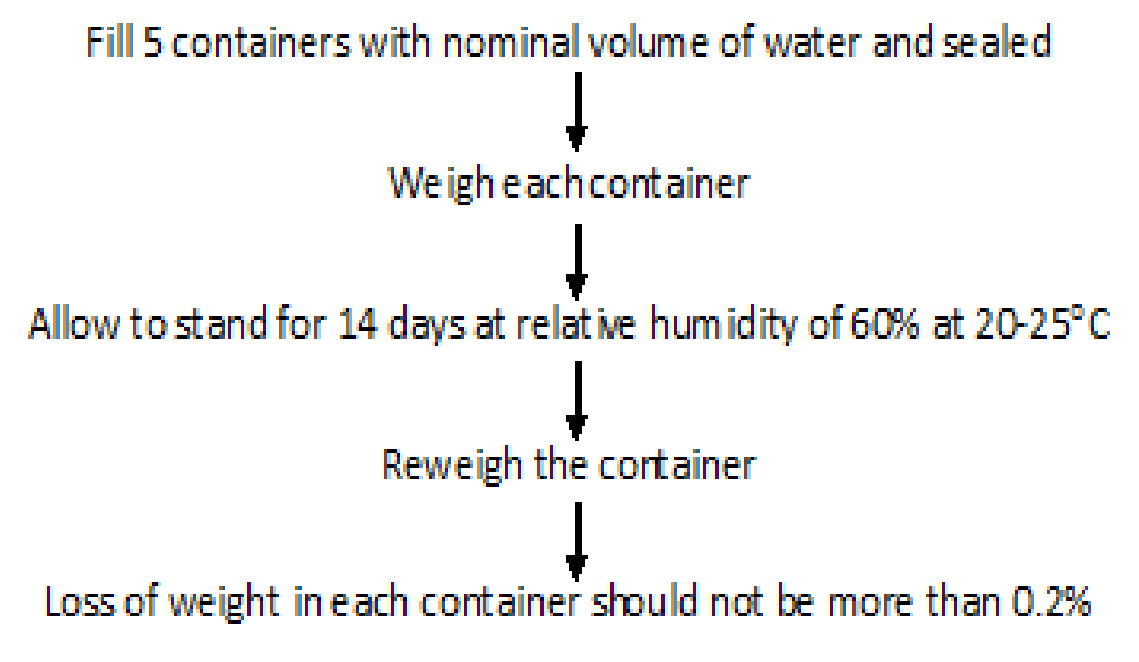
↓

No sign of leakage should be there from any container

2) COLLAPSIBILITY TEST:

- *This test is applicable to the containers which are to be squeezed for removing the contents. A container by collapsing inward during use, yield at least 90% of its normal contents at the required rate of flow at ambient temperature.*

3) WATER PERMEABILITY TEST FOR PLASTIC CONTAINERS (INJECTABLE PREPARATIONS IP 1996):



4) CLARITY OF AQUEOUS EXTRACT:

- *Select unlabelled, unmarked and non laminated portions from suitable containers, taken at random. Cut these portions into strips, none of which has a total surface area of 20sq.cm.Wash the strips free from extraneous matter by shaking them with at least two separate portions of distilled water for about 30sec. In each case and drain off the water thoroughly.*
- *Thus processed sample is taken in to the flask, previously cleaned with chromic acid mixtures and rinsed with several portions of distilled water and added 250ml dist water. Cover the flask and autoclave at 121^{o}C for 30min.Carry out the blank determination using 250ml dist water. Cool and examine the extract, it should be colourless and free from turbidity.*

5) TRANSPARENCY TEST:

- ***Standard suspension preparation**: 1gm hydrazine sulphate in 100ml water and set aside for 6hr. Take 25ml of this solution and add 25ml of 10%w/v hexamine and stand for 24hr.*
- ***Test solution preparation:** Sample is prepared by 16fold dilution of the standard suspension. Fill 5 containers cloudiness detectable when compared to water filled containers. Absorbance is measured at 640nm and the range is within 0.37 and 0.43.*

6) BIOLOGICAL TESTS:

A) Systemic Injection Test:

- *Test animal – Albino Mice*
- *Inject each of 5 mice in test group with sample or blank observe the animals immediately, again after 4hr & then at 24, 48, 72hrs.*
- *If none of animals shows significant greater biological reactivity than the blank the sample meets the requirements.*
- ***Limit**- If abnormal behavior such as Convulsion or Prostration occurs or if body weight loss is greater than 2g, the sample does not meet the requirements.*

B) Intra Cutaneous Test:

- *Test animal- Rabbit*
- *Examine the sites of for any tissue reaction like erythema, oedema, neuosis at 24, 48, 72 hours after injection.*
- ***Limit**- difference between the scores of sample and blank should be lesser than 1.0.*

C) Eye Irritation Test On Rabbits:

- ✓ *Test animal - albino rabbits*
- ✓ ***Limit**- Sample extract shows no significant irritant response during the observation period with blank extract.*

QUALITY CONTROL OF CLOSURES

- ***PREPARATION OF SAMPLE(SOL.-A):*** *Wash closures in 0.2%w/v of anionic surface active agents for 5min.Rinse 5 times with dist water and add 200ml water and is subjected to autoclave at 119 to 123°C for 20 to 30min covering with aluminum foil. Cool and separate solution from closure (soln-A).*

1) STERILITY TEST:

- *When treated closures are subjected to sterilization test at 64-66°C and a pressure of about 0.7 KPa for 24hr.*

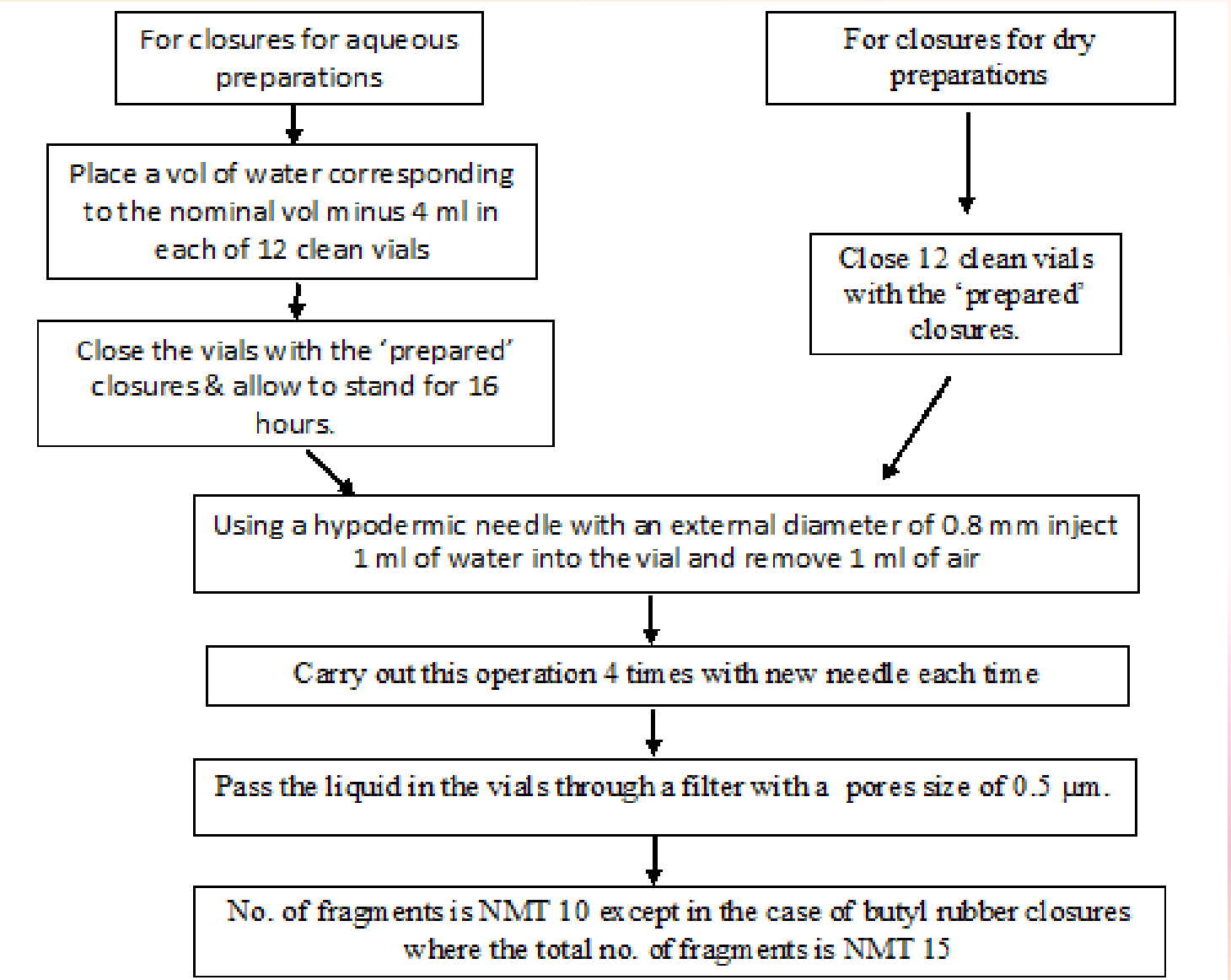
2) RESIDUE ON EVAPORATION:

- *50ml of solution A is evaporated to dryness at 105°C.Then weigh the residue NMT 4mg.*

3) PENETRABILITY:

- *This is measured to check the force required to make a hypodermic needle penetrate easily through the closure. It is measured by using the piercing machine. The piercing force must not exceed a stated value. If it exceeds that stated value, the hypodermic needle can be damaged as a result of undesirable hardness of the closures.*

4) FRAGMENTATION TEST:



5) *Self – sealability:* *This test is applicable to closures intended to be used with water.*

Close the vials with the 'Prepared' closures

↓

For each closure, use a new hypodermic needle with an external diameter of 0.8 mm & pierce the closure 10 times, each time at a different site.

↓

Immerse the vials upright in a 0.1% w/v solution of methylene blue & reduce the external pressure by 27 KPa for 10 min.

↓

Restore the atmospheric pressure and leave the vials immersed for 30 minutes. Rinse the outside of the vials.

↓

None of the vials contains any trace of colored solution.

6) pH OF AQUEOUS EXTRACT:

- *20ml of solution A is added with 0.1ml bromothymol blue when it is added with a small amount of 0.01M NaOH which changes the colour from blue to yellow. The volume of NaOH required is NMT 0.3ml and if it is done with HCl, the volume of HCl needed should NMT 0.8ml.*

7) LIGHT ABSORPTION TEST:

- *It must be done within 4hrs of preparing solution A. It is filtered through 0.5µ filter and its absorbance is measured at 220 to 360nm. Blank is done without closures and absorbance is NMT 2.0.*

8) REDUCING SUBSTANCES:

- *20ml of solution A is added with 1ml of 1M H2SO4 and 20ml of 0.002M KMnO4 and boil for 3 min then cool and add 1gm of potassium iodide which is titrated with sodium thio-sulphate using starch as an indicator. Blank is done and the difference between titration volumes is NMT 0.7ml.*

QUALITY CONTROL OF COLLAPSIBLE TUBES

1) LEAKAGE TEST:

- *Water was filled in the tube and tightly closed. External surface was wiped off and tube is kept inverted on filter paper at base. Allow to stand for 1hr.Filterpaper shows absorption at any time during test period.*

2) LACQUER CURING TEST:

A) Power of adhesion:

- *Tube was spitted along the length and flattened. Cotton wool soaked in acetone was rubbed over lacquer surface for 20min.Lacquer should not lift from surface and cotton wool shall remain colorless.*

B) Flexibility test:

- *The tube was folded in such a manner that internal lacquer surface is outside. The lacquer coating should not be peeled off when the folded position is rubbed with finger.*

3) LACQUER COMPATIBILITY TEST:

- *10 tubes are taken for the test. Product was filled and crimped subjected to 45^{o}C for 72hr.Tubes were allowed to cool and cut lengthwise.*

A) Product compatibility:

- *Content should not show any discolorations or change in colour or gas formation.*

B) Lacquer compatibility:

- *Lifting or peeling of lacquer is checked.*

QUALITY CONTROL OF METALLIC TINS

1) DESCRIPTION:

- *Metallic tins having smooth inner surface. The upper surface is sealed consists a clip to break the seal. The lower surface is open.*

2) DIMENSIONS:

- *Height- Measure the height in mm of 10 metallic tin, individually from the lower surface edge to the upper rim.*
- *Limit- Specimen metallic tins with tolerance-170mm±10mm.*

3) DIAMETER:

- *Inner diameter- Measure the inner diameter of 10 metallic tins.*

Limit- NLT 98mm.

- *Outer diameter: Limit-NMT 105mm.*

4) CLEANLINESS CHECK:

- *It should not be dirty, damaged, stained or consist of any foreign particles.*

QUALITY CONTROL OF STRIP AND BLISTERS

Procedure:

- *3/4th of water is poured in desiccators. The strips and blisters were placed inside the desiccators and vacuum is applied. After sometime vacuum was released and strips, blisters were taken out. The water present over the outer surface of the packages was wiped off with tissue paper. The contents of strips and blister packages were removed and the presence of moisture was checked.*
- *If there is no leakage, the contents will not be wetted. This indicates the perfect sealing of the packages.*

QUALITY CONTROL TESTS FOR CARTONS:

- ***Compression:*** *This method is used to assess the strength of erected package.*
- ***Carton opening force:*** *The method is used to hold the flat carton as delivered, by its creases between thumb & first finger press.*
- ***Coefficient of friction:*** *Both static & kinetic coefficients of friction are determined by sliding the specimen over itself under specific test conditions.*
- ***Crease stiffness:*** *This involves testing a carton board piece & folding it through 90°. It will then try to recover its former position when bending force is removed.*
- ***Joint shear strength:*** *This is a method of testing the glued lap seam on the side of a carton for strength of the adhesive using a tensile testing machine.*

QUALITY CONTROL OF PAPER AND BOARD

- *The tests pieces of paper and board are conditioned for the tests to be carried out in standard conditions.*
- *They are:*
- *Temperature: $23^{o}C \pm 1^{o}C$*
- *Relative humidity: 50%±2%.*
- *Some of the tests to be performed are:*

Name of the Test	Description
Moisture content	All the substances will be measured at temperature specified for test
Folding Endurance	Fold the test piece back & forth until rupture occurs
Density of paper & board	For rigid cellular materials
Method for determining air permeability	Expressed in $\mu m\ pa^{-1}s^{-1}$. It is important for using lightweight uncoated paper on machine having vacuum pick up system
Grammage or substance (g/m^2)	The weight of material per unit area of sample
Paper Caliper	Single sheet thickness between one surface and other

Tensile strength	The maximum tensile force per unit width that a paper or board will withstand before breaking
Tear strength	The mean force required to continue the tearing of an initial cut in a single sheet of paper
Burst strength	The maximum uniformly distributed pressure, applied at right angles to surface that a test piece of paper & board will stand under conditions of test. Hydraulic pressure is applied to diaphragm, bulging it until test piece bursts.
Puncture resistance	Energy required to make initial puncture
Stiffness of thick paper & boards	Degree of resistance offered by paper/board when it is bent
Creasibility of boards	Method to determine creasing quality of board within the range of 300-1000 µm
Cobb test (g/m^2)	Test for water absorbency
Rub resistance	This is resistance of printed test piece to withstand rubbing against another similar test piece
Pick test/IGT test	A specified amount of a special oil is added to the printing system & printed on to the test piece. The surface is then examined for signs of pick.
pH, chloride or sulphate	The acidity or alkality (pH) can help the life of the paper board
Roughness/smoothness	This is very important for 'printablity' of the paper.

Brightness	This is the reflectance factor measured at the effective wavelength of 457 nm
Opacity	This is ratio expressed as percentage of luminous reflectance factor of a single sheet of paper with a black backing to intrinsic luminous reflectance factor.
Dennison wax test	This is a older test and was replaced by the IGT test
Wet burst strength	It is used to determine wet bursting strength of any paper or board following immersion in water
Wet tensile strength	It is to determine wet tensile strength on immersion in water
Ash in paper & board	This is a method of determining the ash content in paper & board
Detection & estimation of nitrogenous agents in paper	It applies only to substances that have a strong affinity for acid dyes
Ink absorbency	The determination of ink absorbency of paper & board by K & N ink.

Quality Assurance Aspects Of Packaging

- *To ensure that patients and consumers receive high-quality drugs, the quality management system must take the following considerations into account if the required quality of packaging is to be obtained:*
  - *— the requirements of the national authorities and the relevant legislation*
  - *— the product*
  - *— the production process*
  - *— the manufacturers' internal policies (safety, marketing, etc.).*

- *Bad packaging which is the result of deficiencies in the quality assurance system for packaging can have serious consequences, and packaging defects can create problems that may result in drug recalls. Such defects may include breakage, and problems relating to printing or inks, or errors on labels and package inserts (patient information leaflets). The use of GMP and quality control will prevent the release of a defective medicinal product.*
- *Packaging processes and equipment need validation/qualification in the same way as any other part of processing within a pharmaceutical facility.*

Sampling and testing of packaging materials

- ***Sampling***

  Sampling is used;

  - *To check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments,*
  - *Detecting adulteration of the medicinal product, obtaining a sample for retention, etc.*
  - *The sampling procedure must take into account the homogeneity and uniformity of the material so as to ensure that the sample is representative of the entire batch.*
  - *The sampling procedure should be described in a written protocol.*

Testing programme

Quality control tests are intended to check the identity of the material concerned. Complete pharmacopoeial or analogous testing may also be carried out, as may special tests, where necessary. All written specifications for packaging materials and containers should include the nature, extent and frequency of routine tests. Routine tests vary according to the type of material and its immediate packaging, the use of the product, and the route of administration. Nevertheless, such tests usually include the following:

- *— visual inspection (cleanliness, defects)*
- *— tests to identify the material*
- *— dimensional tests*
- *— physical tests*
- *— chemical tests*
- *— microbiological tests*

PACKAGE VALIDTAION

Package validation involves two separate validations:

1) The design validation of the package as a component of the device

Design validation uses evidence to establish what design specifications will conform with the user needs and the intended use and

2) The process validation of the packaging process.

Process validation establishes by objective evidence that a process consistently produces a result or product that meets predetermined specifications [820.3(z)(1)].

The regulation, of course, refers to establishing evidence that the manufacturing steps involved in packaging the device will consistently produce packaging which meets specifications. For example, the process capability of packaging and sealing equipment should be determined during process validation and documented. Validation of the package design shall be performed under actual or simulated use conditions that show the package conforms to its stated intended uses. Risk analysis shall also be included where appropriate.

Design validation results shall include: the design identification, name of the individual(s) performing the validation, method(s) used, and the date. All of this information should be recorded in the design history file. If any significant change is made in the packaging or packaging operation after validation, the new process will need to be revalidated.

One of the most difficult aspects of package validation is determining how many samples to test. The goal is not to over test because of cost considerations while still running sufficient tests to provide statistically valid sampling. Statistical methods of analysis are important in process validation. The following decision tree from Medical Device and Diagnostic Industry, "Streamlining Package-Seal Validation," October 1992, provides various methods of statistical analysis. The manufacturer is challenged with determining which statistical method is most applicable to their individual needs. The resulting validation plan should identify, measure, and evaluate the key processes and variables that will require assessment to complete a validation or revalidation of the packaging and the packaging process.

QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS:

- *A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application should contain enough information to show that each proposed container closure system and its components are suitable for its intended use.*
- *The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration.*
- *For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug product for inhalation is often more detailed than that which should be provided about a packaging system for a solid oral dosage form.*

1. Protection:

- *A container intended to provide protection from light or offered as a light-resistant container must meet the requirements of the USP<661> Light Transmission test. The procedure requires the use of a spectrophotometer, with the required sensitivity and accuracy, adapted for measuring the amount of light transmitted by the plastic materials used for the container.*
- *The ability of a container closure system to protect against moisture can be ascertained by performing the USP <661> Water Vapour Permeation test· The USP sets limits to the amount of moisture that can penetrate based upon size and composition of the plastic components (HDPE, LDPE, or PET).*
- *The integrity of the container can be evaluated in several ways.*
- *A couple of the most common tests are dye penetration and microbial ingress. Container closure systems stored in a dye solution and exposed to pressure and vacuum cycles are examined for dye leakage into the container.*
- *The microbial ingress is similar in fashion, but determines the microbial contamination of the contents when soaked in a media contaminated with bacteria.*
- *Other quantitative tests that can be run are vacuum/ pressure decay, helium mass spectrometry, and gas detection.*

2) Compatibility:

- *Components compatible with a dosage form will not interact sufficiently to change the quality of the product or its components.*
- *A leachability study designed to evaluate the amount and/or nature of any chemical migrating from the plastic material to the pharmaceutical product should be implemented. The study should evaluate substances that migrate into the pharmaceutical product vehicle for the length of shelf-life claim.*
- *The drug product should be evaluated at regular intervals, such as at one, three, or six months or at one or two years, until the length of the shelf life claim has been met.*
- *Analytical techniques such as*
  - *Liquid Chromatography/ Mass Spectrometry to evaluate non-volatile organics,*
  - *Gas Chromatography/Mass Spectrometry (GC/MS) to evaluate semi volatile organics, and*
  - *Inductively Coupled Plasma (ICP) spectroscopy to detect and quantitate inorganic elements should be a part of this study.*
- *An infrared (IR) scan of each plastic component should also be included. An IR scan can fingerprint the materials and also provide proof of identity, which will later become part of quality control.*

3) Safety:

- *All packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed during drug treatment.*
- *Isolation is accomplished through sample preparation, followed by incubation in solvents at well-defined and well-controlled times and temperatures.*
- *Some potential extractable chemicals from packaging materials are water soluble, while others are soluble only in non polar environments. For the packaging which are in contact with the drug products, extraction in both polar and non polar environments is relevant.*
- *The USP includes physicochemical tests for plastics based on water extracts; while water, alcohol, and hexane extracts are required for polyethylene containers under controlled temperature and time parameters (70^0C for 24 hours for water and alcohol and 50°C for 24 hours for hexane).*
- *Biological reactivity is the second part of safety testing and is designed to test extractable chemicals for toxicological properties. FDA's guidance document suggests that the USP biological reactivity tests can determine the safe level of exposure via the label-specified route of administration.*

4) Performance:

- *The fourth attribute of suitability of the container closure system, performance and drug delivery, refers to its ability to function in the manner for which it was designed. There are two major considerations when evaluating performance.*
- *The first consideration is functionality that may be to improve patient compliance, minimize waste, or improve ease of use.*
- *The second consideration is drug delivery, which is the ability of the packaging system to deliver the right amount or rate.*
- *Packaging systems that address this consideration are pre filled syringes, trans dermal patches, dropper or spray bottles, and metered-dose inhalers.*

Examples of Packaging Concerns for Common Classes of Drug Products:

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Indictable Suspensions	Sterile powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and lingual Aerosols; Oral Solutions and Suspensions	Topical powders Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

PACKAGE INSPECTION:

- *More critical part of packaging operation is package inspection. In the past this was largely carried out by people under the heading of quality control. With the increase in output of typical packaging lines the inspection task has become difficult for the human person to accomplish. Several important electronics techniques have been developed which allow for the graphic inspection of a number of packaging variables and the rapid rejection of those which to not meet an established standard, and with the passing of those which do.*
- *One notable variable is the accuracy of weight or fill volume. Automatic check weight systems handle all of these. In the case a product sold by volume, a machine-vision system can determine whether the liquid level in a bottle for example is at the proper level.*
- *Labeling is another variable which is regulated. Again machine –vision systems are able to scan each label to be sure that it is correctly applied and that the text is correct for the product being and that the text is correct for the product being packaged.*
- *Metal detection in a product and /or package can be accomplished with several techniques with an X-ray able to detect particulars as small as 0.01 mm at high line outputs.*
- *Leaking packages can be detected at high speed with helium leak detection.*

PHARMACEUTICAL PACKAGE TESTING/ TRANSPORT PACKAGING TESTING:

- ***Transport packaging*** *and their contents are influenced by the modes of transport. Depending on which transport mode that is used, packages will be exposed to different kind of stresses. The main stresses are;*

- ***Mechanical Strains*** *- The most common mechanical strains on transported goods are force stresses like, stacking pressure and shocks and energy stresses like vibration and dropping.*

- ***Climatic Stresses*** *- Climate plays a vital part for the durability and performance of the packaging during the transport.*

- ***Testing Methods***

- *Packaging is tested in two ways;*

1) regarding their material performance

2) how they perform during the actual transportation.

- ***Compression Strength Testing:*** *Packages behave differently when exposed to compressive forces. It uses testing capabilities to apply compressive forces to packages and products and provide a comprehensive report with data on the strength of a package.*

- ***Distribution Simulation Testing:*** *Packages experience many different forces during the shipping and distribution process. It is the product manufacturer's responsibility to evaluate and document the ability of the package to withstand the distribution and storage environments.*

- ***Package Integrity Testing:*** *It uses established tests to test the integrity of a pharmaceutical package. Such tests include dye leak, visual inspection, vacuum leak and bubble leak testing to inspect the package's integrity capabilities.*

- ***Package Strength Testing:*** *Package strength testing is conducted to measure and ensure that the components of the package will not separate when specific forces are applied. The testing of flexible components such as pouches, seal peel or burst testing are methods used to prove the package strength.*

- ***Vibration Testing:*** *Packages and products experience a wide range of dynamic forces and stresses during distribution that could harm the product. It performs vibration tests on samples to simulate the stresses and forces a package or product would experience during the distribution process.*

- ***Shock and Vibe Testing:*** *Dropping, rotational edge dropping and rotational flat drop tests to simulate real world exposure of the package to shock forces by fork lifts, package handling or other factors in the pharmaceutical package's distribution cycle.*

FLEXIBLE PACKAGING:

- *The flexible packaging materials are largely used in Pharmaceuticals for blister packaging of tablets and sachet packing of dispersible powders. Almost 75 % of oral tablets and powders are packaged in US are packaged in flexible materials.*
- *US 21 CFR and USP 34 NF 29 have prescribed a set of specification for controlling the quality of such materials.*
- *Flexible Packaging in context to Pharmaceuticals is non-rigid packaging structures used to package and protect various drug products such as tablets, capsules, powders for medical use.*
- *Flexible packaging covers materials that have undergone a conversion process including printing, lamination, coating and extrusion, and can involve different substrates such as plastic films, paper and foil. Flexible pack types include plastic bags, wrapping films, liding films, aluminium foil laminates; foil liding, blister packaging, foil bags and sachets.*
- *Flexible packaging films can be made from:*

** Single materials such as PE, PP, polyester or PU*

** Multiple materials by coating, laminating or co extruding with the other materials*

- *The most common forms of flexible packaging are the strip package, blister package and the pouch.*

- *A blister package usually consists of a liding material and a forming film.*
- *The liding material is usually a laminate which includes a barrier layer (e.g., aluminium foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side.*
- *The pouch is usually sealed from 3 sides and one side is kept open for filling and sealing thereafter. The sealing agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. Leak testing is usually performed on flexible packages as part of the in-process controls*
- *The most common examples of flexible Pharmaceutical packaging materials are: Aluminium Foil,* ***BOPP (****biaxial oriented polypropylene),* ***LDPE (****low-density polyethylene)* ***LLDPE (****linear low-density polyethylene)* ***OPP*** *(oriented polypropylene)* ***PA (****polyamide)* ***PE*** *(polyethylene)* ***PET*** *(poly ethylene terphthalate),* ***PP (****polypropylene),* ***PVC*** *(poly vinyl chloride) PVDC* ***(****polyvinylidene chloride), as used singly or in laminate form.*

THE BASIC REQUIREMENTS FOR FLEXIBLE PACKAGING MATERIALS AS PER US FDA

- *The product shall be manufactured as per cGMP Guidelines provided under directive 21 CFR parts 11. The products used for as primary packaging of pharmaceutical products shall be manufactured under clean room conditions meeting Class 1,00,000 cleanliness standards.*
  - *The container shall meet all requirements under 21 CFR Direct Food Contact and physical tests in accordance to latest USP <661>:*
  - *The container shall protect the contents from environmental hazard and external influences (e.g. moisture, light, oxygen and temperature variations) during its entire life time beginning from packaging, transportation, handling and storage until use.*
  - *It shall not be composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health*
  - *It shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.*
  - *The integrity of the flexible material must be met throughout the whole of the intended shelf-life of the product. The materials shall be conditioned to the 23°C and 50% RH before conducting any QC/QA tests.*

- *Recycled starting material or finished product is mostly not allowed.*
- *The product shall be supported by Certificate of Analysis (COA) or Certificate of Certification (COC) from the component supplier and the performance of an appropriate identification test, provided the supplier's test data are periodically validated (21 CFR 211.84(d)(3)).*
- *All test methods shall be fully described.*
- *If a batch is to be accepted based on a supplier's COA or COC, then the procedure for supplier validation should be described. The data from the supplier's COA or COC should clearly indicate that the lot meets the applicant's acceptance criteria.*
- *Dimensional information shall be provided via a detailed schematic drawing complete with target dimensions and tolerances*
- *Description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the material.*
- *A complete description of the process and its validation should be provided.*

- ***The following physical tests are performed in accordance to latest USP <661>:***

- ***Multiple internal reflectance's*** *(to ensure that the material of the container falls within the range of HDPE or LDPE as specified in the test),*
- ***Thermal analysis*** *(to check compliance to pre defined endotherms and exotherms temperatures),*
- ***Light transmission*** *(to check protection from light),*
- ***Water vapor permeation*** *(to check protection from moisture permeation)*
- ***Heavy metals,***
- ***Nonvolatile residue.***

SUMMARY OF ICH GUIDELINES ON STABILITY AND POSSIBLE INFLUENCE ON THE PACK:

- *Although the ICH guidelines make reference to stress condition, involving low and high temperatures, low and high humidities, freeze-thaw, varying light intensities, including cycling conditions, storage at a fixed temperature and humidity may not fully challenge the pack (and the product). A pack may therefore withstand continuous storage at 25˚C/60% RH, 30˚C/60% RH, 40˚C/75% RH etc., but fail under cycling or higher temperature stress conditions.*
- *However, packs are more likely to change if exposed to a multiplicity of challenges, e.g. Temperature and RH changes, vibration and compression (on a production line, in storage or distribution), the influence of oxygen, light. Packs which are to some degree permeable to moisture (as are most plastics) will lose or gain moisture according to whether they are exposed to a high or low relative humidity respectively 40˚C/75% RH may be particularly severe on a fully exposed blister pack and give an artificially low shelf life prediction.*

- *Packs removed from a simulated climatic condition also need to be checked for any signs of change/deterioration, prior to opening, during opening (peel strength, closure, torque/force etc.) and after product removal. This is particularly relevant where extremes of temperature and cycling conditions are involved since closure efficiencies may vary according to the storage temperature. This can be critical where a product in its pack is allowed to equilibrate with bench conditions before it is subjected to analysis, so a trained packaging technologist is essential to this examination.*

- *The ultimate task of the pack is to produce confidence in the product in terms of convenience, preservation and protection from the environment. While ensuring that the product remains satisfactory in the fullest sense, i.e. integrity, identity, uniformity, safety, effectiveness etc. all at an economically acceptable art.*


Thank You