

PHARMACEUTICAL PACKAGING, COMPONENT AND EVALUATION



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INTRODUCTION

★ DEFINITION:

Packing: Packing consists of enclosing an individual item, or several items, in a container, usually for shipment or delivery. This operation is mostly done by hand and machine.

Pharmaceutical Packaging: Pharmaceutical packaging means the combination of components necessary to contain, preserve, protect & deliver a safe, efficacious drug product, such that at any time point before expiration date of the drug product, a safe & efficacious dosage form is available.

★ Types of Packaging Systems:

- Primary package system: Made up of those package components & subcomponents that come into direct contact with the product, or those that may have a direct effect on the product shelf life.
- Secondary or tertiary package system: Includes cartons, corrugated shippers & pallets.

★ Packaging must meet the following Requirements: [ideal requirements]

- Protect the preparation from environmental conditions.
- Non-reactive with the product and so does not alter the identity of the product
- Does not impart tastes or odors to the product
- Nontoxic
- FDA approved
- Protect the dosage form from damage or breakage
- Meet tamper-resistance requirements, wherever applicable.
- Adaptable to commonly employed high-speed packaging equipments.

★ Criteria for the Selection of package type and package material:

- Stability
- Compatibility with the contents
- Strength of container and the degree of protection required
- Moisture-proofness
- Resistance to corrosion by Acids or Alkalis
- Resistance to grease
- Protection against salt
- Resistance to microorganisms
- Resistance to insects and rodents
- Resistance to differences in temperature
- Protection against light, fire and pilferage
- Odor retention and transmission
- Aesthetic effect
- Cost
- Machine suitability of packaging and the filling method

- Convenience of the packaging for the physician, pharmacist and finally the patient (size, weight, method of opening/re-closing, legibility of printing)

★ Possible Interactions between primary packaging materials and the included pharmaceutical product:

- The release of chemicals from components of the packaging materials
- The release of visible and/or sub visible particles
- The absorption or adsorption of pharmaceutical components by the packaging materials
- Chemical reactions between pharmaceutical product & the packaging materials
- The degradation of packaging components in contact with the pharmaceutical products
- The influence of the manufacturing process (e.g. sterilization) on the container.

★ Presentation & information

- ✓ Packaging is essential source of information on medicinal product.
- ✓ Information provided to patient may include:
 - Identification no. for dispensing records.
 - Name, strength & quantity
 - Storage instructions.
 - Direction for use.
 - Name and address of dispensers.

★ Compliance

- Help to reinforce the instructions given by physician or the pharmacist and improve compliance with drug therapy.
- Design should be such that product can be easily administered in safer manner to patient.

★ Packaging materials & closures:

- ✓ Glass
- ✓ Plastic
- ✓ Metals
- ✓ Paper and Board
- ✓ Rubber
- ✓ Cotton
- ✓ Adhesives and Inks
- ✓ Closures

★ GLASS CONTAINERS:

Advantages:

1. Superior protective qualities
2. Economical
3. Readily available in a wide variety of sizes & shapes
4. Essentially chemically inert, impermeable, strong and rigid
5. Has FDA clearance
6. Does not deteriorate with age

7. Provides an excellent barrier against every element except light with a proper closure system. Colored glass, especially amber, can give protection against light.

Disadvantages:

1. Fragility
2. Heavy Weight.

Composition of glass

→ Mainly made up of

1. Sand – pure silica
2. Soda-ash – sodium carbonate
3. Limestone – calcium carbonate
4. Cullet – broken glass that is mixed with the batch & acts as a fusion agent for the entire mixture.

The most common cations found in pharmaceutical glassware are silicone, aluminum, boron, sodium, potassium, calcium, magnesium, zinc & barium. The only anion of consequence is oxygen.

TYPES OF GLASS

Type I – Borosilicate Glass

Type II – Treated Soda-Lime Glass

Type III – Regular Soda-Lime Glass

Type NP – General Purpose Soda-Lime Glass

Type I: Borosilicate Glass

- Highly resistant glass
- A substantial part of the alkali & earth cations are replaced by boron and/or aluminum & zinc.
- It is more chemically inert than the soda-lime glass (which contains either none or an insignificant amount of these cations).
- It is used to contain strong acids & alkalis as well as all types of solvents.
- The addition of approx 6% boron to form type I glass reduces the leaching action.

Distilled water stored for 1 year in --	
Type III	Type I
10-15 ppm NaOH	0.5 ppm NaOH

Type II: Treated Soda-Lime Glass

- When glassware is stored for several months, especially in a damp atmosphere or with extreme temperature variations, the wetting of the surface by condensed moisture (condensation) results in salts being dissolved out of the glass. This is called “*blooming*” or “*weathering*” & it gives the appearance of fine crystals on the glass.
- Type II containers are made of commercial soda-lime glass that has been de-alkalized or treated to remove surface alkali.

- The de-alkalizing process is known as “*sulfur treatment*” and virtually prevents “weathering” of empty bottles.
- Some manufactures expose the glass to an atmosphere containing water vapor & acidic gases. This results in a reaction between gases & surface alkali, which makes it resistant to attack by water.
- The alkali removed from the glass appears on the surface as a sulfate bloom, which is removed when the containers are washed before filling.
- *Thus sulfur treatment neutralizes the alkaline oxides on the surface & thus rendering the glass more chemically resistant.*

Type III – Regular Soda-Lime Glass

- Containers are untreated & made up of commercial soda-lime glass of average or better-than-average chemical resistance.

Type NP – General Purpose Soda-Lime Glass

- Containers made up of soda-lime glass are supplied for non-parenteral products, those intended for oral or topical use.

PACKAGE TYPE	TYPE OF FORMULATION CAN BE PACKED	MINIMUM QUALITY OF GLASS THAT CAN BE USED
Ampoule	Aqueous Injectables Of Any pH	Type I
	Aqueous Injectables Of pH Less Than 7	Type II
	Non-Aqueous Injectables	Type III
Vial	Aqueous Injectables Of Any pH	Type I
	Aqueous Injectables Of pH Less Than 7	Type II
	Non-Aqueous Injectables	Type III
	Dry Powders For Parenteral Use (Need To Be Reconstituted Before Use)	Type IV
Bottles and Jars	Tablets, Capsules, Oral Solids & Other Solids For Reconstitution	Type IV
	Oral Liquids (Solutions, Suspensions, Emulsions)	Type IV
	Nasal & Ear Drops	Type IV
	Certain Types Of External Semisolids (Rubeficients, Local Irritants)	Type IV
	Blood & Related Products	Type I

Dropper	Auxiliary Packaging Device With Certain Kind Of Products	Type IV
Aerosol container	Aerosol product (solution, suspension, emulsion or semisolid type)	Type I

★ PLASTIC CONTAINERS:

Advantages:

1. Ease of manufacturing
2. Available in various types of quality
3. Freedom of design to which they lend themselves
4. Extremely resistant to breakage

TABLE: Polymers used for the production of Plastics:

COMMONLY USED POLYMERS	LESS COMMONLY USED POLYMERS
Polyethylene	Polymethyl methacrylate
Polypropylene	Polyethylene terephthalate
Polyvinyl chloride (PVC)	Polytrifluoroethylene
Polystyrene	Aminoformaldehydes
	Polyamides

Dosage Form – Plastic Interactions / Limitations of Plastic Materials:

1. Permeation
2. Leaching
3. Sorption
4. Chemical modification
5. Alteration on the properties of plastics or product

1. Permeation

- The transmission of gases, vapors or liquids from the surrounding environment into the plastic container is known as “*Permeation*”.
- Permeation of water vapor & oxygen through the plastic wall into the dosage form can be problematic if the drug is sensitive to hydrolysis and/or oxidation.
- An increase in temperature, increases permeability of gases.
- An increase in crystallinity of the material decreases permeability.
- Hydrophilic plastic materials such as nylon are poor barriers to water vapor, while hydrophobic materials like polyethylene are better barriers.
- The concentration of drugs in formulations containing volatile ingredients might change when stored in plastic containers because of the permeation of one or more volatile ingredients through the walls of the plastic containers.

- Plastic containers also affect the physical properties of the product. For example, when water-in-oil emulsion is stored in a hydrophobic plastic bottle, there is a tendency for the oil phase to migrate & diffuse into the plastic.
- Permeation may also affect the shelf-life of a drug.

2. Leaching:

- Release of a constituent from the plastic material of the container into the formulation is known as “*leaching*”.
- For example, particular dyes which are used as coloring agents may migrate into a product, contaminates the product and may cause a toxic effect.

3. Sorption:

- The Process of extraction / removal of one or more of the constituents from the formulation by the packaging material are referred to as “*Sorption*”.
- Becomes a serious problem particularly for dosage forms that contain drug and/or other important ingredients in the solution form.
- May significantly affect the therapeutic efficacy of the formulation containing highly potent drug.

4. Chemical reactivity:

- Certain ingredients used in plastic container manufacturing may chemically react with one or more components of a drug product.
- These chemically incompatible substances may also alter the appearance of the plastic or formulation.

5. Modification:

- The physical or chemical alteration of the packaging material by the drug product is called “*modification*”.
- The content may extract the plasticizer, antioxidant or stabilizer, thus changing the flexibility of the container.
- Permeation, sorption or leaching may also alter the properties of the plastic container. For example: (1) Oils have a softening effect on polyethylene; (2) Fluorinated hydrocarbons attack polyethylene & PVC.

CHARACTERISTICS OF VARIOUS PLASTIC MATERIALS -

Properties	<u>Polyethylene</u>		Poly Propylene	PVC	Poly Styrene	Acrylic Multi-Polymer	Nitrile Polymer
	Low Density	High Density					
Clarity	Hazy, Translucent	Hazy, Translucent	Clear	Clear	Clear	Clear	Clear
Water Absorption	-	-	-	-	+, ++	+	+, ++
Permeability To							
Water Vapor	-	--	--	- +	++	++	+
Oxygen	++	+, ++	+, ++	-	++	-	--
CO ₂	++	+, ++	+, ++	-	++	+	--

Resistance To							
Acids	+, +++	+, +++	+, +++	+++	+, ++	-, ++	-, ++
Alcohol	++	++	++	+++	-	+	+
Alkalis	++	++	+++	++	++	-, ++	++
Mineral Oil	-	+	+	++	+	++	+++
Heat	-	+	++	+, -	+	++	+
Cold	++++	++++	-, +	--	-	-	-
Sunlight	+	+	+	++	+, -	++	++
High Humidity	++++	++++	++++	++++	++++	+	++++
Stiffness	-	+	+, ++	+, ++	+, ++	+, ++	+, ++
Cost	Low	Low	Low	Mod	Low	Mod	High
Typical Uses	Cosmetics Personal Products Foods	Detergents Bleaches Milk Foods Industrial Cleansing Powders Drugs Cosmetics	Drugs Cosmetics Syrups Juices	Shampoos Bath Oils Detergents Whisky Wine Floor Waxes Vinegar Salad Oil	Dry Drugs Petroleum Jellies	Foods Drugs Cosmetics	Foods Drugs Cosmetics Chemicals Aerosols Carbonated Beverages

Signs: [- - : very poor, very low] [- : poor, low] [+ : fair, moderate] [++ : good, high] [+++ : very good] [++++ : excellent]

★ METAL CONTAINERS:

- Aluminum & stainless steel are the metals of choice for both primary & secondary pharmaceutical packaging.
- Form excellent tamper-evident containers.
- Metals are strong, impermeable to gases & shatterproof, so they are ideal packaging material for pressurized containers.

PACKAGE TYPE	FORMULATION	REMARKS
Strip, blister	Tablets, capsules	Polymer coated aluminum with various thickness are available to improve the sealability of the pack and stability of the product.
Collapsible tubes	Ointments, creams, gels & other semisolids	The tubes with internal protective coating of polymers with spike & without spike are available.

Cans	Aerosols, inhalers, sprays etc.	Pressure resistant and internal polymer coated aluminum containers are available.
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★ PAPER & BOARD:

- The paper-based materials are the important part of pharmaceutical packaging.
- Paper-based materials include: 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 & 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.

★ RUBBER based components:

➤ Mostly used to make stoppers and bulbs for dropper assemblies.

⇒ Examples of rubber for pharmaceutical products include:

1. Natural rubber
2. Neoprene rubber
3. Nitrile rubber
4. Butyl rubber
5. Chlorobutyl rubber
6. Bromobutyl rubber
7. Silicone rubber

★ COTTON:

PACKAGE TYPE	REMARKS
Wadding	In solid preparations to prevent the collision of individual units or to absorb moisture etc.
As Desiccant	To Prevent absorption of moisture particularly by tablets & capsules from environment.

★ ADHESIVES and INKS:

- ⇒ Some substances, such as cements and lacquers used as label adhesives, are not water-based emulsions. They are usually dissolved in toluene, alcohol, naphtha, methyl ethyl ketone, or other organic solvents.
- ⇒ When an adhesive of this type is used on plastics or elastomers, the solvent may allow migration of adhesive components into the formulation. Therefore, appropriate testing should be performed to determine whether adhesive and ink components migrate through the container. If they do, adequate information to justify the use of the container system in combination with the drug product should be submitted.
- ⇒ For all containers, testing should be conducted on the effectiveness of the adhesive under appropriate challenge conditions (e.g., temperature and humidity).
- ⇒ If direct label imprinting is used on containers, such as on containers of injectable drug products, it is necessary that resistant ink be used so that the imprint having the required information resists the normal handling of the containers during their customary conditions of purchase and use.

★ CLOSURES

- Depending upon the type of container, closures may have different shapes & sizes.
- Special design of stopper may also be required for some pharmaceutical production processes such as lyophilization.
- Closures, which form a part of the primary packaging system, are very important & should be therefore carefully selected. They form essential component of the container & an integral part of the drug preparation.

Closures generally require consideration of the following factors:

- Resistant & compatible with the product & the product/air space.
- If closure is re-closable, it should be readily openable & effectively resealed.
- Capable of high-speed application for automatic production by high speed machines without loss of seal efficiency.
- Decorative & of a shape which blends in with the main container.
- Offers such additional functions: aid-pouring, metering, administration, child resistance, tamper evidence, etc.
- Prevents exchange with the outside atmosphere to a permissible level.

The majorities of closure systems are incorporated by physical compression or heat sealing. The *physical compression system* includes:

- 1) Screw caps – In metal or plastic, preheated or rolled on with or without a wadding system (i.e. wadless). Wad is a mass of soft material used to stop hole.
 - 2) Plug in – A friction push in fit
 - 3) Push over – A flanged or raised ring portion is pressed over a bead or lip.
- Wadless thermoplastic caps using a ‘crab’s claw’ seal or a skirted bore seal are very popular.
 - Wadded screw caps either contain a wad plus a facing, a disc of resilient plastic or have a flowed-in plastic compound.
 - The wad may be of compo-cork, felt-board, and pulp-board or expanded PE, faced with such materials as aluminum foil, tin foil, PE, PVC.
 - These have good barrier properties and are reasonably inert, and most widely used these days.
 - Foil or waxed foils are less preferable if a higher barrier material is required.
 - Rolled on (RO) or rolled on Pilfer Proof (ROPP) aluminum alloy metal caps are popular for security of export products.
 - RO and ROPP closure consists of a plain metal shell containing wadding or flowed-in system, which is placed over the container neck & pressure is applied on top to give a good impression on the wad.
 - In case of pilfer proof closure; an additional perforated collar is ruled under a lower bead. This type of closure system is capable of maintaining an excellent seal & does not suffer from the occasional tearing of the wad when a conventional screw cap is applied to a substandard bottle finish.

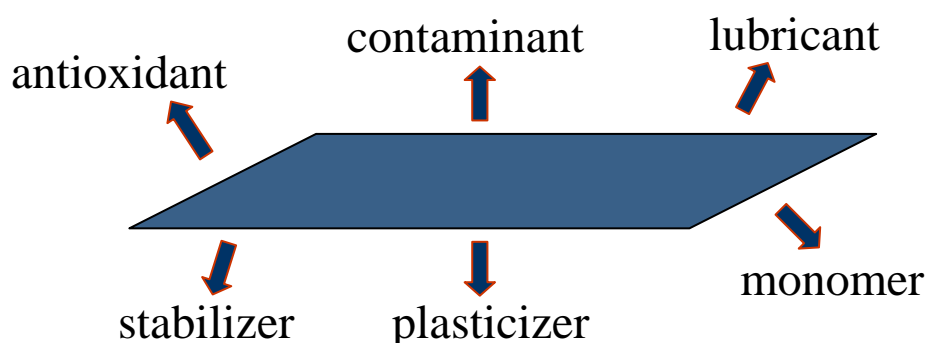
Functions of a closure:

1. Hermetic seal: Permits no exchange between the contents & the outside of the pack, e.g. a fused glass ampoule.
2. Effective microbiological seal e.g. rubber cork & metal overseal.
3. Effective seal, acceptable to the product.

Packaging Evaluation:

Package evaluation is performed to investigate the physicochemical interactions that might occur between the product & package. The ideal package would be completely inert relative to the product & would provide maximum shelf-life. Therefore, evaluation is designed to identify, characterize & monitor these interactions to achieve a safe, unadulterated, stable & efficacious product.

- ❑ An important step -- characterizing the materials and the chemicals that can migrate or extract from packaging components to the drug product.
- ❑ Figure shows the various types of chemicals that can migrate from polymeric materials. The identities and abundance of these chemicals determine a material's suitability.



- ✓ A number of tests can be used to establish *initial qualification* of the container closure system, and a *quality control plan* can help ensure compatibility and safety.
- ✓ To establish suitability, evaluation of four attributes is required: protection, compatibility, safety, and performance/ drug delivery.
- ✓ Suitability refers to the tests used for the initial qualification of the container closure system with regard to its intended use.

⇒ Table - Properties of suitability concerns and interactions.

Attributes	Concerns and Interactions	Proposed Methods
Protection	Exposure to light, moisture, microbial ingress, and oxidation from presence of oxygen	USP<661> Light Transmission and Water Vapor Permeation, Container Integrity (Microbial Ingress, Dye Penetration, Helium Leak)
Compatibility	Leachable-induced degradation, absorption or adsorption of drug, precipitation, changes in pH, discoloration, brittleness of packaging materials	Leachability Study (Migration of chemicals into drug product) using LC/MS, GC/MS, ICP/AA, pH, appearance of drug and container, thermal analysis (DSC, TGA), & IR
Safety	No leached harmful or undesirable amounts of substances to expose patients treated with drug	Extraction study (USP Physicochemical Tests-Plastics), USP Elastomeric Closures for Injections, Toxicological Evaluation USP Biological Reactivity and complies with CFR additives and purity
Performance	Container closure system functionality, drug delivery	Functionality (improved patient compliance or use) Delivery (transfer dose in right amount or rate)

Suitability testing should be able to establish the following criteria:

- Materials of construction of container and closure components are safe for their intended use.
- Container components are compatible with the dosage form. The container and closure system adequately protects the dosage form. The entire system functions in the manner in which it is intended.

Quality Control

- ✓ After demonstrating container closure system suitability, it is necessary to define *quality control measures* that will be used to ensure consistency in the packaging components.
- ✓ Dimensional criteria such as shape, volume, wall thickness, and design tolerances should be defined and monitored.
- ✓ Physical considerations such as water vapor transmission to evaluate seal integrity, thermal analysis such as DSC to monitor melting point and glass transitions of plastics, and IR scanning to prove identity should be a part of an ongoing quality-control monitoring program.
- ✓ Chemical composition should also be evaluated by performing the simple but informative USP physicochemical tests using water, drug product vehicle, and alcohol extractions of plastic components.

The ultimate goal of the evaluation is to eliminate or control any interactions that are discovered so that they are rendered innocuous. Whereas, secondary package influences product stability, it must be included in the evaluation.

TABLE: Dosage forms and package forms

DOSAGE FORM	CONDITION	ROUTE OF DELIVERY	POSSIBLE PACKAGE FORM
Solids (Tablets, Capsules, Powders)	Non-Sterile	Oral	- Glass Or Plastic Bottle And Cap - Blister And Strip Packaging - Sachet, Pouches - Drums And Jars
Solids	Non-Sterile	Rectal (Suppository)	- Foil Pouch Or Blister
Solids	Aseptic	Inhalation	- Dry-Powder Inhaler
Liquids	Non-Sterile	Oral	- Glass Or Plastic Bottle And Cap - Bottle With Spray Pump - Bottle With Dropper Assembly - Sachet, Pouches - Drums And Jars
Liquids	Non-Sterile	Topical	- Glass Or Plastic Bottle And Cap Over Dropper Tip - Collapsible Tube - Aerosol Sprays - Drums And Jars
Liquids	Sterile	Parenteral, Ophthalmic	- Glass Ampoules - Glass Or Plastic Vial With Stopper - Glass Or Plastic Vials With Applicators

			- Pre-Filled Syringe - Bag - Pre-Filled Form-Fill-Seal Plastic Container
Ointments, Creams	Non-Sterile	Topical	- Collapsible Tube - Pump (High Viscosity Dispenser) - Transdermal Delivery Device - Glass Or Plastic Jar
Ointments	Sterile	Ophthalmic	- Collapsible Tube - Glass Or Plastic Bottle And Cap - Form-Fill-Seal Plastic Bottle - Glass Or Plastic Jar - Soft Gelatin Capsules

Packaging of MEDICAL / SURGICAL DEVICES

- The medical device packages are usually evaluated to meet the following requirements:
- They must be capable of being sterilized economically.
- They must withstand the shipping and handling environment.
- They must be compatible with the procedures set up by the hospitals.
- Sterility
- Environmental
- Product resistance: oils, water, chemicals, gas, etc.
- Physical: Dimensional stability (rigidity or flexibility, resists puncture, tearing, abrasion, impact and pressure, provides cushioning and structural support.

Evaluation of Medical Device Packages:

- The Medical Device Packages Testing Laboratory is set up with the following principle goals:
- To evaluate the component materials of container and the inner protective cushioning materials
- To develop (through research) improved methods or concepts and improved package testing techniques.

The types of tests carried out for Medical Device Packages are as follows:

- Sterility Testing
- Manual handling
- Vehicle stacking
- Loose-load vibration
- Vehicle vibration
- Drop test
- Compression
- Package seal strength testing

ECONOMIC ASPECTS AND OUTLOOK

The investigator responsible for the package design must have a broad background in a variety of disciplines. A solid foundation in the areas of chemistry, regulatory affairs, pharmaceutical dosage forms, material-science and package engineering is essential. Cost savings may include both direct and indirect costs through improved accuracy of the data, shorter project timing, reduced project costs (because fewer stability studies are needed) and reduced packaging material costs.

With the advent of new dosage forms, new materials and new drug classes (such as those produced through bio-engineering), the package may be the most important factor in bringing the product to the marketplace.

A delivery system that brings convenience at a lower cost to the users (physicians, pharmacists and patients) is a major factor for success in a market place where efficiency has already been demonstrated.

REGULATORY ASPECTS OF PHARMACEUTICAL PACKAGING

INTRODUCTION:

- ➔ About 90 % of all PRODUCT RECALLS are caused by FAULTY PACKAGING AND LABELLING.
- ➔ Those products recall results in loss of thousands of money for industry so now a day industry are putting more and more concern about the accuracy and efficacy of the pharmaceutical packaging and labeling.
- ➔ Can we afford to be making this many errors? The answer is no.
- ➔ For that almost all the regulatory agencies are providing stricter specifications for the packaging and labeling of the pharmaceuticals.

CHILD RESISTANT PACKAGING

- ➔ The provision of child-resistant packaging for pharmaceutical products is an emotive subject.
- ➔ The packaging that excludes the entry of children of less than 5 years age but not adults to access the contents of the pack.
- ➔ Legally : “ at least 80% of children between the ages of 20 and 42 months forming a test panel are unable to open the packaging within 5 minutes of receiving it”
- ➔ Up to now, all standards for testing for child-resistant compliance give a definition of such a package as being the immediate packaging which is resistant to opening by children (under 52 months old), but which does not pose difficulties for the elderly (over 65 years) to open and, where appropriate, to re-close properly.

REGULATION OF CRP IN UK

- ➔ Consumer groups in Europe are campaigning for standards for child resistance compliance to be brought more in line with the US protocol.
- ➔ The Child Safety Packaging Group in the UK is pressing for unit dose pharmaceutical packaging to be tested for child resistance.
- ➔ The British Standards Institution (BSI) will introduce standards.
- ➔ The Medicines Control Agency (MCA) are currently reviewing The UK Medicines (Child Safety) Amendment Regulations 1994, which will call up this standard and the products requiring child-resistant packaging are likely to be extended.

The American Society for Testing and Materials (ASTM) gives a list of:

Classifications of child-resistant packages

- Type I: Reclosable packaging - continuous thread closure
- Type II: Reclosable packaging - lug finish closure
- Type III: Reclosable packaging - snap closure
- Type IV: Unit non-reclosable - flexible (strip/pouch)
- Type V: Unit non-reclosable - rigid
- Type VI: Unit reclosable packages
- Type VII: Aerosol packages
- Type VIII: Non-reclosable packages - semi-rigid (blister)
- Type IX: Dispensers (not intended to be removed)
- Type X: Box or tray package
- Type XI: Reclosable packaging - flexible
- Type XII: Dispenser (may be removed)
- Type XIII: Reclosable packaging - semi-rigid (blister)

TESTING PROTOCOL FOR CHILD RESISTANT PACKAGING

REQUIREMENTS:

- ❖ On full scale production batch
- ❖ Adult test must be carried out initially
- ❖ A new package must be used for every test
- ❖ Test panel may involve upto 200 children in the ages between 20 and 42 months, almost equally distributed between either sex.
- ❖ 100 normal adults between 18 and 65

METHODOLOGY:

- ❖ Adults are asked to open within 5 minutes using the direction that appear on the package and reclose it if it is reclosable type.
- ❖ Then children are asked to open totally for 10 minutes after being demonstrated by an adult.
- ❖ For full 10 minutes 80% of the children shall not be succeeded in opening
- ❖ In 5 minutes 90% of the adults must be successful in opening.

TAMPER PROOF PACKAGING

- ◆ Tamper proof containers are those that resist the tampering of the product before consumer the product.
- ◆ They help in....
 - ❖ Receiving the products by patients “ as manufactured “
 - ❖ Preventing “ product browsing and sampling “

TAMPER PROOF CONTAINERS

- Film Wrappers
- Blister or Strip Packs
- Bubble Packs
- Heat Shrink Bands or Wrappers
- Foil, Paper, or Plastic Pouches
- Bottle Mouth Inner Seals
- Tape Seals
- Breakable Caps
- Sealed Metal Tubes or
- Plastic Blind-end Heat Sealed Tubes
- Cans
- In-Built Tamper-Evident Controls

REGULATION OF PHARMACEUTICAL PACKAGING COMPONENTS**WHY THERE IS A REQUIREMENT FOR REGULATION OF PHARMACEUTICAL PACKAGING MATERIALS?**

As mentioned earlier most of the product recalls are due to faulty packaging and labeling. And that results in much of the industrial loss. Any problem related to the faulty packaging and label ling will result in potential health hazard, so regulatory agency of the all countries provides guidelines to be followed for the packaging and labeling of the pharmaceutical and biologicals used for the human and animals.

- ◆ There is a great number of regulatory requirements on pharmaceutical packaging materials, in
 - The pharmacopoeias,
 - The GMP regulations, in
 - The FDA guidance, &
 - Other regulatory guidance.
- ◆ New guidances by FDA and othe regulatory agency for labeling, packaging and nomenclature may help in providing suitable pharmaceutical packing with the aim of providing the package for a specific drug will preserve the drug`s efficacy as well as its purity, identity, strength, and quality for its entire shelf life.
- ◆ It must be emphasized that packaging preserves the stability and quality of medicinal products and protects them against all forms of spoilage and tampering.
- ◆ FDA doses not approve containers as such, but only the materials used in the containers and give them the standard of “Generally Regarded As Safe”. (GRAS)
- ◆ The pharmaceutical manufacturer has to guarantee that only such packaging materials are used that are
- ◆ Correctly printed,
 - ✓ Means it should state what it contain and it should contain what it should state.
- ◆ In conformity with the specifications and

- ◆ In compliance with the regulatory requirements.

FDA 'S CURRENT FOCUS:

- CMC CC PACKAGING TECHNICAL COMMITTEE:
- PACKAGING GUIDANCE COMMITTEE:
- CMC CC RECENT PACKAGING INITIATIVE:

CMC CC- Chemistry, Manufacturing and Control Coordinating Committee

CMC CC PACKAGING TECHNICAL COMMITTEE

It includes various offices from CDER, CBER and CVM.

- **CDER - Centre For Drug Evaluation And Research**
 - Office Of New Drug Chemistry
 - Office Of Generic Drug
 - Office Of Compliance
 - Office Of Testing And Research
 - Quality Implementation Staff
- **CBER- Centre For Biological Evaluation And Research**
 - Office Of Compliance And Biologics Quality
- **CVM – Centre For Veterinary Medicine**
 - Office Of New Animal Drug Evaluation

PACKAGING GUIDANCE COMMITTEE

- ✓ Disentwining the packaging information to CDER, CBER, and CVM.
- ✓ Reviewing pharmacopoeial forum packaging proposal
- ✓ Internal guidance and comment to
 - Reviewer
 - CMC CC committee
 - CTDQ document
- ✓ External guidance via CMC CC PACKAGING equivalency test
- ✓ Drafting revision to packaging guidance bulk container , Q and A format

PHARMACOPOIEAL FORUM

It provides information for the following,

- Injection
- Elastomer clouser for injections
- Container
- Cotton filler
- Rayon filler
- Packaging practice:

- Repackaging of single solid oral drug product in to unit dose container

PACKAGING GUIDANCE COMMITTEE:

- Packaging Guideline, 1987
- Packaging Guidance, 1999
- WHO Technical Report Series, No. 902, Annex 9,
 - Guidelines on packaging for pharmaceutical products, 2002

PACKAGING IN OTHER GUIDELINES

- Stability Testing of Drug Substances and Drug Products, draft, 1998
Packaging for solid and liquid oral drugs
- ICH Common Technical Document-Quality (CTD-Q) S.6 and P.2.4
- EN 13427:2004
Packaging - Requirements for the use of European Standards in the field of packaging and packaging waste
- The Federal Food, Drug, and Cosmetic Act : Section 501-505
- The Code Of Federal Regulation : 21 CFR 211
(Subpart E, Subpart F, Subpart G)
- 16 CFR 1700-1702 – Special Packaging
- Compliance Policy Guides That Concerns Packaging :
Subpart 410, 430, 440-448, 450-457, 480

PACKAGING GUIDANCE 1999

- This document is intended to provide guidance on general principles for submitting information on packaging materials used for human drugs and biologics.
- All necessary documents are submitted to regulatory authority considering the various aspects covered in guideline.
- Also the additional information regarding the contract packager and repackager, if any than should be provided as and when needed.
- Represents Company's current thinking on container closure systems for packaging of human and biological products.
- Does not create or confer any rights for or on any person and does not operate to bind FDA or the public.
- An alternative approach may be used if such approach satisfies the requirement of the applicable status, regulation or both.
- Provide guidance on general principles for submitting information on packaging materials used for human drugs and biologics

PACKAGING COMPONENTS:

1. Primary components:

- Syringes ,
- ampoules ,
- flexible bags,

- bottles and
 - Clousers
2. Secondary components:
- Cartons and
 - overlaps
3. Associated components:
- Dosing droppers and
 - calibrated spoon

QUALIFICATION AND QUALITY CONTROL OF PHARMACEUTICAL PACKAGING COMPONENTS

INTRODUCTION:

- A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for the 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.
- 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

TABLE 1:
EXAMPLES OF PACKAGING CONCERNS FOR COMMON CLASSES OF DRUG PRODUCTS

Degree of Concern Associated with the Route of administration	PACKAGING COMPONENT-DOSAGE FORM INTERACTION		
	HIGH	MEDIUM	LOW
HIGHEST	Inhalation Aerosol and Solution ; Injectables	Sterile powder and powder of injection	
HIGH	Ophthalmic solution, susp., Transdermal Patches, nasal sprays		

LOW	Topical solution ,susp. Aerosol, Oral sol.,susp.	Topical Powders Oral Powders	Oral Tablets and Capsule
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GENERAL CONSIDERATIONS

1. DESCRIPTION

2. SUITABILITY

- Suitability refers to the tests and studies used and accepted for the initial qualification of a component or a container closure system for its intended use.
- Every proposed packaging system should be shown to be suitable for the intended use. It should protect and compatible and composed of material that are considered as safe for use with dosage form.
- An adequately detailed description of the tests, methods, acceptance criteria, reference standards, and validation information

3. PROTECTION

- A container closure system should be providing the dosage form adequate protection against cause of degradation like: light, temp, loss of solvent, exposure to reactive gases, microbial contamination. Not every drug product is susceptible to degradation by all of these factors.
- Laboratory studies can be used to determine which of these factors actually have an influence on a particular drug product.
- I.e. If light protection is required opaque or amber colored container are used and if protection against microbes is essential then maintain adequate integrity after packaging and during packaging.

4. COMPATIBILITY

- Compatibility between packaging component and the drug substance and excipients should be determined.
- Absorption or adsorption cause loss of potency, brittleness of packaging component and leaching can lead to degradation, precipitation, change in drug pH, discoloration
- Some of Such interaction will be detected during qualification studies and investigated and appropriate action should be taken.

5. SAFETY

- Components should not leach harmful substance to which a patient will be exposed when being treated with drug products.
- For injection, inhalation, ophthalmic, or transdermal, a comprehensive study is appropriate like Extraction study on the packaging components to determine which chemical species may migrate in to dosage form and then toxicological evaluation of those substances

- The approach for toxicological evaluation of the safety of extractable should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).

6. PERFORMANCE

- Ability to function in the manner for which it was designed. Evaluation of performance include:
 - i. Container closure system functionality
 - The container closure system may be designed to improve patient compliance (e.g., a cap that contains a counter), minimize waste (e.g., a two-chamber vial or IV bag), improve ease of use (e.g., a prefilled syringe), or have other functions.
 - ii. Drug delivery
 - Drug delivery refers to the ability of the packaging system to deliver the dosage form in the amount or at the rate described in the package insert.
 - Some examples of a packaging system for which drug delivery aspects are relevant are a prefilled syringe, a transdermal patch, a metered tube, a dropper or spray bottle, a dry powder inhaler, and a metered dose inhaler.

7. QUALITY CONTROL

8. STABILITY

TABLE 2 :TYPICAL SUITABILITY CONSIDERATIONS FOR COMMON CLASSES OF DRUG PRODUCTS

Route of Administration/ Dosage Form	SUITABILITY ^a			
	Protection	Compatibility	Safety	Performance/ Drug Delivery
Inhalation Aerosols and Solutions, Nasal Sprays	L, S, M, W, G	Case 1c	Case 1s	Case 1d
Inhalation Powders	L, W, M	Case 3c	Case 5s	Case 1d
Injections, Injectable Suspensions ^b	L, S, M, G	Case 1c	Case 2s	Case 2d
Sterile Powders and Powders for Injection	L, M, W	Case 2c	Case 2s	Case 2d
Ophthalmic Solutions and Suspensions	L, S, M, G	Case 1c	Case 2s	Case 2d
Topical Delivery Systems	L, S	Case 1c	Case 3s	Case 1d
Topical Solutions and Suspensions, and Topical and Lingual Aerosols	L, S, M	Case 1c	Case 3s	Case 2d
Topical Powders	L, M, W	Case 3c	Case 4s	Case 3d
Oral Solutions and Suspensions	L, S, M	Case 1c	Case 3s	Case 2d

PROTECTION

L = protects from light, if appropriate

S = protects from solvent loss/leakage

M = protects sterile products or those with microbial limits from microbial contamination

W = protects from water vapor, if appropriate

G = protects from reactive gases, if appropriate

COMPATIBILITY:

Case 1c: Liquid-based dosage form that conceivably could interact with its container closure system components

Case 2c: Solid dosage form until reconstituted; greatest chance for interacting with its container closure system components occurs after it is reconstituted.

Case 3c: Solid dosage form with low likelihood of interacting with its container closure system components

SAFETY:

Case 1s: Typically provided are USP Biological Reactivity Test data, extraction/toxicological evaluation, limits on extractable and batch-to-batch monitoring of extractable.

Case 2s: Typically provided are USP Biological Reactivity Test data and possibly extraction/toxicological evaluation.

Case 3s: Typically, an appropriate reference to the indirect food additive regulations is sufficient for drug products with aqueous based solvents. Drug products with non-aqueous based solvent systems or aqueous based systems containing co-solvents generally require additional suitability information

Case 4s: Typically, an appropriate reference to the indirect food additive regulations is sufficient.

Case 5s: Typically, an appropriate reference to the indirect food additive regulations for all components except the mouthpiece for which USP Biological Reactivity Test data is provided.

PERFORMANCE:

Case 1d: Frequently a consideration.

Case 2d: May be a consideration.

Case 3d: Rarely a consideration.

QUALITY CONTROL OF PACKAGING COMPONENTS

- It is used to ensure consistency in the packaging components. These controls are intended to limit unintended post approval variation in the manufacturing procedures or materials of construction of packaging component and to prevent adverse affects on the quality of dosage forms.

PRINCIPLE CONSIDERATION

PHYSICAL CHARACTERISTICS

- Dimensional criteria like shape, neck finish, wall thickness
- Physical parameter like unit weight
- Performance like metering valve delivery volume

- Unintended variation in dimensional parameters if undetected, may affect package permeability, drug delivery performance, or adequacy of seal between container and closure.

CHEMICAL COMPOSITION

May affect safety, compatibility, functional characteristics or protective properties

Composition change may occur due to...

Change in formulation or processing aid

Change in manufacturing process

TABLE 3:- INFORMATION THAT SHOULD BE SUBMITTED IN SUPPORT OF AN ORIGINAL APPLICATION FOR ANY DRUG PRODUCT

Description	Overall general description of the container closure system plus <u>For each packaging component :</u> <ul style="list-style-type: none"> • Name, Product code, Manufacturer, Physical description • Materials of construction • Description of any additional treatments or preparation. 				
Suitability	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> Protection : ✓ Light exposure ✓ Reactive gases ✓ Moisture permeation ✓ Solvent loss ✓ Microbial contamination ✓ </td> <td style="width: 50%; vertical-align: top;"> Safety : ♦ Chemical composition ♦ Extractables ♦ Extraction/toxicological study ♦ Other studies as appropriate </td> </tr> <tr> <td style="vertical-align: top;"> Compatibility : ❖ Interaction ❖ Post approval stability studies </td> <td style="vertical-align: top;"> Performance : → Functionality → Drug delivery </td> </tr> </table>	Protection : ✓ Light exposure ✓ Reactive gases ✓ Moisture permeation ✓ Solvent loss ✓ Microbial contamination ✓	Safety : ♦ Chemical composition ♦ Extractables ♦ Extraction/toxicological study ♦ Other studies as appropriate	Compatibility : ❖ Interaction ❖ Post approval stability studies	Performance : → Functionality → Drug delivery
Protection : ✓ Light exposure ✓ Reactive gases ✓ Moisture permeation ✓ Solvent loss ✓ Microbial contamination ✓	Safety : ♦ Chemical composition ♦ Extractables ♦ Extraction/toxicological study ♦ Other studies as appropriate				
Compatibility : ❖ Interaction ❖ Post approval stability studies	Performance : → Functionality → Drug delivery				
Quality Control	For Each Packaging Component Received by the Applicant <ul style="list-style-type: none"> ➤ Applicant`s test and acceptance criteria ➤ Dimensional and performance criteria ➤ Method to monitor consistency in composition For Each Packaging Component Provided by the Supplier <ul style="list-style-type: none"> ➤ Manufacturer`s acceptance criteria for release ➤ Brief description of Mfg. Process 				
Stability	Container closure system should be monitored for sign of instability. Applicant should investigate any observed change In the packaging system used in stability studies. If corrective action requires a change in an approved container closure system, a supplemental application should be submitted.				

TABLE 4: INFORMATION FOR INJECTION AND OPHTHALMIC DRUG PRODUCTS

Description	<p>Overall general description of container closure system</p> <p><u>For Each Packaging Component :</u></p> <ul style="list-style-type: none"> ✓ Name, Product code, Manufacturer, Physical description ✓ Materials of construction ✓ Procedures for sterilizing and depyrogenating packaging components
Suitability	<p>Protection : Compatibility :</p> <ul style="list-style-type: none"> ➤ Light exposure ✓ Coating integrity testing ➤ Reactive gases ✓ Evaluation of swelling effects for elastomeric ➤ Moisture permeation ✓ Physicochemical tests for Plastic ➤ Solvent loss ✓ Particulate matter & eye irritation for Ophtha. ➤ Sterility ➤ Seal integrity <p>Safety :</p> <ul style="list-style-type: none"> ✓ Chemical composition ✓ USP elastomeric Closure for injection testing ✓ USP Containers : chemical Resistance- glass containers ✓ USP biological Reactivity Test –plastic components ✓ Extraction profile <p>Performance :</p> <ul style="list-style-type: none"> ✓ Functionality and / or drug delivery
Quality Control	<p>For Each Packaging Component Received by the Applicant</p> <ul style="list-style-type: none"> ✓ Applicant`s test and acceptance criteria ✓ Dimensional and performance criteria ✓ Method to monitor consistency in composition of plastic & elastomer ✓ For Each Packaging Component Provided by the Supplier ✓ Manufacturer`s acceptance criteria for release ✓ Brief description of Mfg. Process

TABLE 5:- AAO RECOMMENDED COLOR CODING OF CAPS AND LABELS FOR TOPICAL OPHTHALMIC MEDICATION:

COLOR CODING

USP supports the suggestion that the use of color-coding for pharmaceutical Products to prevent medication errors are used cautiously and on a case-by-case basis

CLASS	COLOR
Anti-infectives	Tan
Anti-inflammatories/ Steroids	Pink
Mydriatics and Cycloopegics	Red
NSAIDs	Gray
Miotics	Green
Beta Blockers	Yellow or Blue

Suitability	Protection : As per last table → LDPE & Glass-USP container testing microbial contamination → Coating integrity testing Compatibility : Safety : Tablet, Capsule : appropriate reference to indirect food additive regulation Rayon and cotton filters : USP monograph Dessiccants: size and shape should differ from that of dosage form Performance : Functionality and/or drug delivery
Quality Control	As per last table
Stability	As per last table

OTHER DOSAGE FORMS

- ✓ Compatibility & safety concerns raised by route of administration and nature
- ✓ Kind of protection the container should provide to dosage form
- ✓ Potential effect of any treatment or handling that may be unique to the drug product in the packaging system.

POST APPROVAL PACKAGING CHANGES

- For an approved application (NDA, ANDA, BLA) a change to
 - ✓ A container closure system,
 - ✓ A component of the container closure system,
 - ✓ A process involving one of the above
 must be reported to the application.
 - ✓ A material of construction for a component

TYPE III DRUG MASTER FILE:

A. GENERAL COMMENTS

B. INFORMATION IN A TYPE III DMF

- The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA or BLA, or the sponsor of an IND.
- This information may be provided to the applicant by the manufacturer of a packaging component or material of construction and may be included directly in the application.
- Any information that a manufacturer does not wish to share with the applicant or sponsor (i.e., because it is considered proprietary) may be placed in a Type III DMF and incorporated into the application by a letter from the manufacturer to the applicant which authorizes reference to the DMF

DESCRIPTIVE INFORMATION:

- General description of the component and the address of the manufacturing site

- Description of the manufacturing process for a packaging component and operations performed after manufacture, but prior to shipment
- Description of the acceptance, in-process, and release controls for materials of construction, the manufacturing process, and the finished product
- Characterization of the key

INFORMATION ABOUT SUITABILITY

- Protection provided by the component
- Safety information on the materials of construction or the finished component
- Compatibility of the materials of construction or the finished component with the specific dosage form, the specific drug product, or equivalent materials

INFORMATION ABOUT QUALITY CONTROL:

- Dimensional (an engineering drawing) and performance criteria for the component
- A description of the quality control measures used to maintain consistency in the physical and chemical characteristics of packaging components
- A summary of the quality assurance/quality control criteria when release of the component is based on statistical process control

FDA REGULATIONS

REGULATORY REQUIREMENTS

The Federal Food, Drug, and Cosmetic Act

(a) Section 501:

“A drug or device shall be deemed to be adulterated “ if its container is composed, in whole or part, any poisonous or deleterious substance which may render the contents injurious to the health “ (section 501(a)(3))

(b) Section 502:

- ✓ A drug or device shall be deemed to be misbranded
- ✓ → If it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed manner (502(g))
- ✓ → If it is a drug and its container is so made, formed, or filled as to be misleading (502 (i)(1))
- ✓ → If it is a drug and packaging or labeling is in violation of an applicable regulation issued pursuant to section 3 or 4 of the Poison Prevention Packaging Act of 1970

2. Subpart F : Production & Process Control (21 CFR 211.100-211.115)

3. Subpart G : Packaging and Labeling Control (21CFR 211.122-211.137)

- 21 CFR 211.132 describes the Tamper Resistant packaging requirements for OTC human drug products.

(b) 16 CFR 1700-1702 – Special Packaging

- The U.S consumer Product Safety Commission (CPSC) is responsible for enforcing the Poison Prevention Packaging Act (PPPA) in 1970. The PPPA requires special packaging of hazardous household substance to protect children from serious injury or serious illness from handling, using.
- Which Pdt requires Special Packaging?

- Human oral prescription
- OTC drug preparation
- PPPA regulation establishes performance standards and test methods that determine if a packaging system is child resistant and adult use effective.

COMPLAINCE POLICY GUIDES THAT CONCERNS PACKAGING

Subpart 410:- Bulk Drugs

410.100: Finished Dosage forms drug pdt. In bulk container

Subpart 430:- Labeling and Repackaging

430.100: Labeling for solid and liquid oral dosage forms

430.200: Repackaging of drug pdts.- Testing/examination under CGMP

Subpart 440-448:- New Drugs

446.100: Regulatory action regarding Approved New Drug and Antibiotic drug pdt.

Subjected to Additional Processing or Manipulations.

Subpart 450-457:- OTC

450.500: Tamper Resistant packaging requirements for certain OTC human drug products

450.550: Control and accountability of labeling associated with Tamper

Resistant packaging of OTC drug products.

Subpart 480:- Stability / Expiration

480.100: Requirements for expiration Dating and stability testing

480.200: Expiration dating of unit dose Repackaged drugs

480.300: Lack of Expiration date of Stability data

EXTRACTION STUDY

- Involves exposing a sample of component to an appropriate solvent system at elevated temperature, followed by chemical analysis.
- Methods depends on : Purpose of extraction
: Nature of packaging component
- HPLC or GC used for qualitative or quantitative extraction profile of volatile or non volatile extractable.

Why Extraction studies may be conducted during the qualification of packaging components?

- To perform USP characterization test on plastic or elastomer
- To perform Biological Reactivity test on plastic or elastomer
- To obtain quantitative extraction profile
- To obtain qualitative extraction profile
- To evaluate whether FDA indirect food additive regulation provide an adequate indicator of safety

QUALITY SPECIFICATION BY WHO:

REQUIREMENTS FOR THE DOSAGE FORM CONTAINERS:

- TABLETS
- CAPSULES
- PARENTERAL PREPARATION
- TOPICAL SEMI-SOLID DOSAGE FORMS

(A) Requirements in the International Pharmacopoeia :**Requirements for the Dosage form Containers:****TABLETS:**

- Kept in well closed container & protected from light, moisture, crushing and mechanical shock.
- Additional special recommendations for packaging, storage, transportation are specified in relevant individual monographs (Eg. Effervecent Tablet)

CAPSULES:

- Packaged and stored in a manner that protects them from microbial contamination.
- Should be protected from light, excess moisture, or dryness

PARENTERAL PREPARATION:

- Usually supplied in glass ampoules, bottles or vials , plastic bags and PFS which are colored in case of light sensitive substance.
- Mostly containers are transparent to permit visual inspection
- Closure should be equipped with a firm seal to prevent entry of microbes.
- A tamper evident container is fitted with a device.

TOPICAL SEMI-SOLID DOSAGE FORMS:

- Containers should be made from a material that does not adversely affect the quality of the preparation
- Containers should be of a design that minimizes microbial contamination.
- Use of suitable metal or plastic flexible tubes is preferred.
- The preparation should maintain its pharmaceutical integrity throughout the shelf life when stored at the temperature indicated on the label.

STUDY QUESTIONS:

- Define: Packing and Pharmaceutical Packaging. (Uni. 2006)
- What are the criteria for the selection of materials for pharmaceutical packaging? (Uni. 2006)
- Give details of glass as the packaging material.
- Short note : Evaluation of pharmaceutical container closure system.
- Write a note on CRP or TEP. What is AAO recommendation for color coating.
- write note on DMF. (1st test 2006)
- Write a note on child resistant and temper proof packages. (Uni. Exam. 2006 & 07)

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- Plastic Packaging , *Remington: The Science and Practice of Pharmacy*, 19th edition, Volume II, p 1487.
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