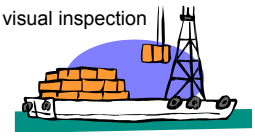
Container and Package Materials

- Learning objectives
- Demonstrate knowledge of different package materials and their use and compatibility with drugs
- Define USP containers
- Define USP storage conditions
- Required readings: Ansel p 71, 80-90

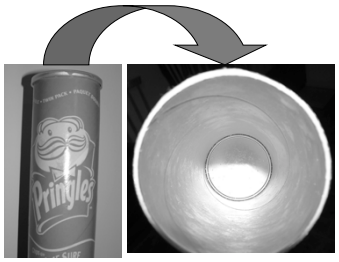
Container and Package Materials

- Inert material
- Withstand temperature change and mechanical use
- Protect the content from radiation
- Protect the content from microbiological contamination
- Should be transparent for visual inspection
- Inexpensive
- Space for label
- Facilitate storage



Containers

- The USP classifies containers in its *General Notices and Requirements* according to their ability to protect their contents from external conditions.

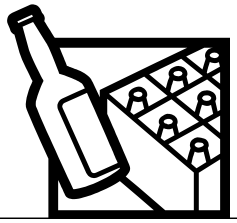


Basic Container classes

- **USP container**: "that which holds the article and is or may be in direct contact with the article"
- **Immediate container**: "that which is in direct contact with the article at all times"
- Child resistant/child proof

Basic Container classes

- Well-Closed Container—A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.



Basic Container classes

- Tight container: protect the content from contamination by extraneous liquids, solids or vapors, from loss from efflorescence, deliquescence evaporation under ordinary conditions
- tight re-closure!

Basic Container classes

- Hermetic container: impervious to air or any other gas under the ordinary or customary conditions

- Sterile vial for single use
- Withdraw of article without changing the quality,purity, strength of article

Hermetic containers

- Sterile hermetic containers are generally used to hold preparations intended for injection or parenteral administration.
- A **single dose** container is one that holds a quantity of drug intended as a single dose and when opened cannot be resealed with assurance that sterility has been maintained.
- These containers include fusion sealed ampoules and prefilled syringes and cartridges.
- A **multiple-dose** container is a hermetic container that permits withdrawal of successive portions of the contents without changing the strength or endangering the quality or purity of the remaining portion.
- These containers are commonly called vials.

USP Container Classes

- Single-Dose Container: is a single-unit container for articles intended for parenteral administration only.
- Multiple-Dose Container: is a multiple-unit container for articles intended for parenteral administration only.

USP Container Classes

- Unit-Dose Container: is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

USP Container Classes

- Multiple-Unit Container: is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Storage

To ensure the stability of a pharmaceutical preparation for the period of its intended shelf life, the product must be stored in proper conditions. The labeling of each product includes the desired conditions of storage. The terms generally employed in such labeling have meanings defined by the USP:

Storage

Cold: Any temperature not exceeding 8°C (46°F).

- A refrigerator is a cold place in which the temperature is maintained thermostatically between 2° and 8°C (36° and 46°F).
- A freezer is a cold place in which the temperature is maintained thermostatically between -25° and -10°C (-13° and 14°F).

Cool: Any temperature between 8° and 15°C (46° and 59°F). An article for which storage in a cool place is directed may alternatively be stored in a refrigerator unless otherwise specified in the individual monograph.

Storage

Room temperature: The temperature prevailing in a working area. A controlled room temperature encompasses the usual working environment of 20° to 25°C (68° to 77°F) but also allows for temperature variations between 15°C and 30°C (59° and 86°F) that may be found in pharmacies, hospitals, and drug warehouses.

Warm: Any temperature between 30° and 40°C (86° and 104°F).

Excessive heat: Above 40°C (104°F).

Storage

Protection from freezing: Where in addition to the risk of breakage of the container, freezing subjects a product to loss of strength or potency or to destructive alteration of the dosage form, the container label bears an appropriate instruction to protect the product from freezing.

USP Container

<660> CONTAINERS-GLASS
<661> CONTAINERS-PLASTICS
<671> CONTAINERS-PERFORMANCE TESTING
<681> REPACKAGING INTO SINGLE-UNIT CONTAINERS AND UNIT-DOSE CONTAINERS FOR NONSTERILE SOLID AND LIQUID DOSAGE FORMS

USP Container

<660> CONTAINERS-GLASS

Chemical resistance

Type	General Description	Type of Test
I	Borosilicate glass	Powdered Glass
II	Treated soda-lime glass	Water Attack
III	Soda-lime glass	Powdered Glass

USP Container

<661> CONTAINERS-Plastics

POLYETHYLENE CONTAINERS
POLYPROPYLENE CONTAINERS
POLYETHYLENE TEREPHTHALATE BOTTLES AND CONTAINERS

<661> CONTAINERS-Plastics

Test Methods
IR
DSC differential scanning calorimetry
Biological Tests
Physicochemical Tests
- •Air permeability
- •Leaching into plastic material
- •Surface adsorption
- •Light transmission
- •Plasticizer

<661> CONTAINERS-Plastics

Test Methods
Biological Tests
(biological reactivity of mammalian cell cultures following contact with the elastomeric plastics and other polymeric materials)

Grade	Reactivity	Conditions of all Cultures
0	None	Discrete intracytoplasmic granules; no cell lysis
1	Slight	Not more than 20% of the cells are round, loosely attached, and without intracytoplasmic granules; occasional lysed cells are present
2	Mild	Not more than 50% of the cells are round and devoid of intracytoplasmic granules; no extensive cell lysis and empty areas between cells
3	Moderate	Not more than 70% of the cell layers contain rounded cells or are lysed
4	Severe	Nearly complete destruction of the cell layers

<671> CONTAINERS-PERFORMANCE TESTING

- MULTIPLE-UNIT CONTAINERS FOR CAPSULES AND TABLETS
- Procedure— Select 12 containers of a uniform size and type
- open each container 30 times.
- Close screw-capped containers with a torque
- Add Desiccant to 10 of the containers, designated test containers
- To each of the remaining 2 containers, designated controls, add a sufficient number of glass beads to attain a weight approximately equal to that of each of the test containers.
- Record the weight

<671> CONTAINERS-PERFORMANCE TESTING

- MULTIPLE-UNIT CONTAINERS FOR CAPSULES AND TABLETS
- store at 75 ± 3% relative humidity and a temperature of 23 ± 2.
- After 336 ± 1 hours (14 days), record the weight of the individual containers
- determine the average container volume, in mL.
- Calculate the rate of moisture permeability, in mg per day per L, by the formula:
- (1000 / 14V)[(TF – TI) – (CF – CI)]

<671> CONTAINERS-PERFORMANCE TESTING

- MULTIPLE-UNIT CONTAINERS FOR CAPSULES AND TABLETS
- For containers used for drugs being dispensed on prescription, the containers so tested are tight containers if not more than one of the 10 test containers exceeds 100 mg per day per L in moisture permeability, and none exceeds 200 mg per day per L.
- For containers used for drugs being dispensed on prescription, the containers are well-closed containers if not more than one of the 10 test containers exceeds 2000 mg per day per L in moisture permeability, and none exceeds 3000 mg per day per L.

Special tests

- Container for Ophthalmic preparations
  - Metal Particles

681 REPACKAGING INTO SINGLE-UNIT CONTAINERS AND UNIT-DOSE CONTAINERS FOR NONSTERILE SOLID AND LIQUID DOSAGE FORMS

- In lieu of dispensing two or more prescribed drug products in separate containers, a pharmacist may, with the consent of the patient, the patient's caregiver, or a prescriber, provide a customized patient medication package (patient med pak).

CUSTOMIZED PATIENT MEDICATION PACKAGES

- A patient med pak is a package prepared by a pharmacist for a specific patient comprising a series of containers and containing two or more prescribed solid oral dosage forms.
- The patient med pak is so designed or each container is so labeled as to indicate the day and time, or period of time, that the contents within each container are to be taken.

CUSTOMIZED PATIENT MEDICATION PACKAGES

Labeling

- The patient med pak shall be accompanied by a patient package insert, in the event that any medication therein is required to be dispensed with such insert as accompanying labeling.
- Alternatively, such required information may be incorporated into a single, overall educational insert provided by the pharmacist for the total patient med pak.

CUSTOMIZED PATIENT MEDICATION PACKAGES

Packaging

- In the absence of more stringent packaging requirements for any of the drug products contained therein, each container of the patient med pak shall comply with the moisture permeation requirements for a Class B single-unit or unit-dose container.
- Each container shall be either not reclosable or so designed as to show evidence of having been opened.

Container Classes <671>

- Class A if not more than 1 of 10 containers tested exceeds 0.5 mg per day in moisture permeation rate and none exceeds 1 mg per day;
- Class B not exceeds 5 mg per day and none exceeds 10 mg per day
- Class not exceeds 20 mg per day and none exceeds 40 mg per day;
- Class D if the containers tested meet none of the moisture permeation rate requirements.

CUSTOMIZED PATIENT MEDICATION PACKAGES

Guidelines

- It is the responsibility of the dispenser, when preparing a patient med pak, to take into account any applicable compendial requirements or guidelines and the physical and chemical compatibility of the dosage forms placed within each container, as well as any therapeutic incompatibilities that may attend the simultaneous administration of the medications.
- In this regard, pharmacists are encouraged to report to USP headquarters any observed or reported incompatibilities.
- Once a medication has been placed in a patient med pak with another solid dosage form, it may not be returned to stock, redistributed, or resold if unused.
- It is the responsibility of the dispenser to instruct the patient or caregiver on the use of the patient med

CUSTOMIZED PATIENT MEDICATION PACKAGES

Label— The patient med pak shall bear a label stating:

1. the name of the patient;
2. a serial number for the patient med pak itself and a separate identifying serial number for each of the prescription orders for each of the drug products contained therein;
3. the name, strength, physical description or identification, and total quantity of each drug product contained therein;
4. the directions for use and cautionary statements, if any, contained in the prescription order for each drug product therein;
5. any storage instructions or cautionary statements required by the official compendia;
6. the name of the prescriberr of each drug product;
7. the date of preparation of the patient med pak and the beyond-use date or period of time assigned to the patient med pak (such beyond-use date or period of time shall be not longer than the shortest recommended beyond-use date for any dosage form included therein or **not longer than 60 days from the date of preparation of the patient med pak** and shall not exceed the shortest expiration date on the original manufacturer's bulk containers for the dosage forms included therein); alternatively, the package label shall state the date of the prescription(s) or the date of preparation of the patient med pak, provided the package is accompanied by a record indicating the start date and the beyond-use date;
8. the name, address, and telephone number of the dispenser (and the dispenser's registration number where necessary); and any other information, statements, or warnings required for any of the drug products contained therein.

If the patient med pak allows for the removal or separation of the intact containers there from, each individual container shall bear a label identifying each of the drug products contained therein.

CUSTOMIZED PATIENT MEDICATION PACKAGES

Recordkeeping— In addition to any individual prescription filing requirements, a record of each patient med pak shall be made and filed. Each record shall contain, as a minimum:

1. the name and address of the patient;
2. the serial number of the prescription order for each drug product contained therein;
3. the name of the manufacturer or labeler and lot number for each drug product contained therein;
4. information identifying or describing the design, characteristics, or specifications of the patient med pak sufficient to allow subsequent preparation of an identical patient med pak for the patient;
5. the date of preparation of the patient med pak and the beyond-use date that was assigned;
6. any special labeling instructions; and
7. the name or initials of the pharmacist who prepared the patient med pak.

1191 STABILITY CONSIDERATIONS IN DISPENSING PRACTICE

- In general, repackaging is inadvisable.
- However, if repackaging is necessary, the manufacturer should be consulted concerning potential problems. In the filling of prescriptions, it is essential that suitable containers be used. Appropriate storage conditions and, when appropriate, an expiration date and beyond use date should be indicated on the label of the prescription container.

1191 STABILITY CONSIDERATIONS IN DISPENSING PRACTICE

- Single-unit packaging calls for care and judgment and for strict observance of the following guidelines:
- (1) use appropriate packaging materials,
- (2) if stability data on the new package are not available, repackage at any one time only sufficient stock for a limited time,
- (3) include on the unit-dose label a lot number and an appropriate beyond-use date,

1191 STABILITY CONSIDERATIONS IN DISPENSING PRACTICE

- (4) if a sterile product is repackaged from a multiple-dose vial into unit-dose (disposable) syringes, discard the latter if not used within 24 hours, unless data are available to support longer storage,
- (5) if quantities are repackaged in advance of immediate need, maintain suitable repackaging records showing name of manufacturer, lot number, date, and designation of persons responsible for repackaging and for checking (see *General Notices*),
- (6) if safety closures are required, use container closure systems that ensure compliance with compendial and regulatory standards for storage.

Basic Container materials

All glass	ampoule
Glass + elastomer	vial, bottle, syringe
All plastic	ampoule, bag
Plastic + elastomer	bottle, syringe
Plastic + metal foil	bag

USP-Basic Container materials

- Glass
  - Cheap
  - heat resistant
  - transparent
- Plastic
  - Thermoplastics
  - Thermosetting plastic
    - flexible
    - many shapes
    - Chemical exchange with dosage form!
    - Risk of incompatibility

Glass

- relatively chemically inert
- reactions affected by
  - type and agitation of solution,
  - washing procedures,
  - thermal history,
  - current temperature,
  - glass composition and
  - storage time
- solutions of alkalis cause separation of glass flakes from the walls of the container over time
- yields soluble mineral substances into aqueous injections
  - **1. Precipitation eg. alkaloids, polypeptides**
  - **2. Decreased stability, alkaloids, polypeptides**

Flaking

Parts of a silica-rich layer produced on the surface of glass containers as a result of alkali extraction fall away can be seen as glistening flakes

Flakes are produced most readily by alkaline solutions because these roughen the surface by eating away parts of the silica.

Thermal Resistance and Mechanical Strength

Glass containers must be strong enough to withstand risks of normal handling and transport some must also be able to resist hazards of sharp change in temperature and pressure ie. injections sterilised by heating methods, including steam under pressure at the end of sterilisation by autoclaving the pressure inside the apparatus falls to atmospheric pressure and then the lid is removed or door is opened sudden contact of cool air from the room with very hot contents which cool slowly due to poor thermal conductivity of their glass walls may cause breakages due to high pressure inside the closed container, can occur with explosive violence

Glass Types

Resistance to release of minerals into distilled water

Type I: High Hydrolytic Resistance Boro-Silicate Glass

neutral or borosilicate glass (increase B and Al oxides)

injectable preparations, may be re-used

Glass Types

Lime-Soda Glass

Type II -high hydrolytic resistance

treat surface with moist SO_2 at 500°C

injectable preparations not for re-use and others.

Type III - moderate hydrolytic resistance

packaging of liquid preparations not in an aqueous vehicle and for powders to be reconstituted immediately before use.

Glass Types

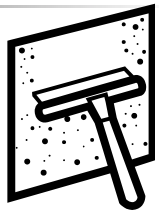
Neutral Glass

Lead-free Glass

Silicone Treated Glass

QC of Glass Container materials

- Light transmission
- Chemical resistance
- Powdered glass test
- Water attack at 121^{0}C
- Arsenic



660 CONTAINERS glass test

CHEMICAL RESISTANCE—GLASS CONTAINERS

- Apparatus—
- *Autoclave*— For these tests, use an autoclave capable of maintaining a temperature of 121 ± 2.0 , equipped with a thermometer, a pressure gauge
- Special Mortar and Pestle for Pulverizing Glass

- *Other Equipment*— Also required are 20.3-cm (8-inch) sieves made of stainless steel including the Nos. 20, 40, and 50 sieves along with the pan and cover
- 250-mL conical flasks made of resistant glass aged as specified
- a 900-g (2-lb) hammer, a permanent magnet, a desiccator, and an adequate volumetric apparatus.

660 CONTAINERS glass test

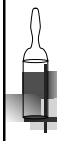
CHEMICAL RESISTANCE—GLASS CONTAINERS

- Crush the containers into fragments about 25 mm in size and heat treat it and tirate the alkaline substances

Summary of Glass

- Soda Lime Glass (III)
  - Soft and chemically not very resistant
  - Thermal shock
  - Anhydrous , dry content
- Surface treated Glasses (II)
  - 500 ^{0}C sulfur oxide
- Borosilicate Glass (I)
  - Boron + aluminum oxides
  - Better chemical resistance and shock resistant
  - Higher price, higher melting point
- NP not for Parenterals
- Boron, magnesium, barium, potassium, zinc salts, iron, titanium

Example Parenteral Containers



Ampoule

thin wall; glass or polyethylene or polypropylene, sealed by fusion; single use

Vial

thin to medium wall; rubber stopper; single or multiple use

Pre-filled syringes and cartridges

set

Plastic

Plastics are in regular use for packaging certain types of sterile products including infusion and dialysis fluids eye-drops and injections ready-filled disposable syringes

Plastics: General Properties

1. **Synthetic polymers of high molecular weight**
2. **Sensitive to heat, may melt or soften below 100°C some plastics can be autoclaved eg. nylon, polycarbonate, polypropylene, and high density polyethylene**
3. **Light in weight, easier to handle, make transport cheaper**
4. **Mechanically almost as strong as metals, containers can have thinner walls than needed for glass.**
5. **Poor conducters or heat, disadvantage if container and contents require heat sterilization.**

Plastics: General Properties

6. **Resistant to inorganic chemicals but often attacked by organic substances, eg. solvents and oils.**
7. **Contain antioxidants, lubricants, plasticizers, stabilizers. Some substances can be leached out into solutions stored in plastic containers. Chemical bonding between the medication or preservatives in the solution and chemicals in the plastic,can reduce the strength or stability of the former.**
8. **Very few types completely prevent the entry of water vapour at all temperatures to which an injection container may be exposed. Some are permeable to gases, eg. oxygen and CO_2**

Thermoplastic

- A plastic that can be repeatedly softened by heating and hardened by cooling through a temperature range

Types of Plastics

Thermoplastics

Soften to a viscous fluid on heating which hardens on cooling Hardness when cooled is influenced by the degree of cross-linking or intermolecular attraction between long-chain molecules

Nylon and high density polyethylene produces more rigid material while polystyrene and polymethylacrylate are hard and somewhat brittle at room temperature because of strong forces

Thermoplastics

1. **Polyethylene**
2. **High Density Polyethylene**
3. **Polyvinyl Chloride**
4. **Polymethylmethacrylate**
5. **Polystyrene**
6. **Polytetrafluroethylene**
7. **Polypropylene**
8. **Polyamides**
9. **Polycarbonate**

Thermosetting Plastics

- A plastic that, when cured by application of heat or by chemical means, changes into a substantially infusible and product

Thermosetting

When heated, these may become flexible but they do not become fluid and their shape is retained right upto the temperature of decomposition.

Due to a high-degree of cross linking they are usually hard and brittle at room temperature.

1. **Phenol-formaldehyde**
2. **Urea-formaldehyde**
3. **Melamine-formaldehyde**

Plastics

high-density polyethylene (HDPE)
Invented by Robert L. Banks and J. Paul Hogan, 1951.
Uses: plastics of all kinds, high-strength fibers

DuPont Tyvek®

low-density polyethylene (LDPE)
Invented by Eric Fawcett and Reginald Gibson, 1935.
Uses: plastic films, bags

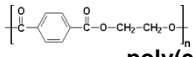
Plastic materials

- Polyethylene (not heat resistant)
- HDPE (High-Density Polyethylene):
- HDPE is characterized by its rigidity, low cost, ease of forming, and resistance to breakage. It is used to bottle milk, water, juices, bleach, detergents, and motor oil.
- This plastic is usually either cloudy white, allowing light to pass through it (natural) or a solid color, preventing light from passing through it (colored).

Plastic materials

- Polyethylene (not heat resistant)
- LDPE (Low-Density Polyethylene)
- LDPE is widely used in applications requiring clarity and processing ease. Its most common use is as film for grocery sacks.
- No Plasticizers!!!
- CH_3-(CH_2 - CH_2)$_n$ - CH_3

Plastics



poly(ethylene terephthalate) (PETE)
Invented by J.R. Whinfield and J.T. Dickson, 1940.

Uses: clothing, plastic films, plastic bottles

Plastic materials

- PETE (Polyethylene Terephthalate):
- PETE, a commonly recycled household plastic material, represents approximately 30 percent of the plastic bottle market and is used to package a wide variety of food and beverage products such as soft drinks, juices, edible oils, liquor and peanut butter. PETE is valued for its clarity, toughness, and ability to resist permeation by carbon dioxide.

poly(vinyl chloride)
Invented by Waldo Semon, 1926.
Uses: water pipes, LP records, vinyl car tops

Plastics

polypropylene (PP)
Invented by Robert L. Banks and J. Paul Hogan, 1951.
Uses: fibers for rope, indoor-outdoor carpeting, plastics

Plastic materials

- Polyvinyl Chloride - PVC
- Clear
- Up to 30% plasticizer (Dioctylphthalate)
- Highly permeable to oxygen and water
- Blood collection bags
- Not useful for radiation sterilization
- CH_3-(CHCl - CH_2)$_n$ - CH_3

Plastic materials

- Polypropylene - PP
- Clear
- No plasticizers
- Brittle at low temperatures
- Can be autoclaved
- CH_3-(CH CH_3 - CH_2)$_n$ - CH_3

Plastics

polystyrene (PS)
Invented by Eduard Simon, 1839.
Uses: rigid plastics of all kinds, polystyrene foams

anything else, including items made from more than one kind of polymer

Plastic
Nylon
Polyamide

PA has a good strength (fishing line, axe handle), wear resistance (bearings), barrier properties (food packaging) and machinability. Strength and stiffness are often improved using glass fibre reinforcement.

PA absorbs water which makes it softer. **UV-stabilizators** are required for outdoor applications.

PA is a group of amorphous (transparent) and semi-crystalline (opal-white) plastics. The latter are distinguished by a numeric code indicating the number of carbon atoms between two nitrogen atoms in the molecular chain (e.g. PA6 and PA11).

Polymethylmethacrylate “Plexiglass”

softens at 100°C
asceptic screens
contact lenses
heart and lung machines

Polydimethylsiloxane silastic

Closures, tubes, diaphragms,
implants, contact lens
less interactions

Polytetrafluoroethylene (Teflon)

extreme resistance to heat to 200°C
semi-rigid
slippery and non-wettable

Plastic materials

- Polymethylpentene
  - High temperature resistant 160 ^{0}C
  - Expensive

Plastic materials

- Polycarbonate
  - High temperature resistant
  - Brittle
  - Compatible with Ethyleneoxide
- Polyesters
  - Beverage bottles
  - Material of the future?
- Copolymers
  - Saran (PE + Latex)
  - PVC – Aluminium foil

Rubber

- (CH2 - C = CH - CH2) -
  CH3

- natural polymeric material with many additives
- closures
- treat with silicone derivatives to reduce interactions
- particulate and microbial contaminants
- many interactions

Types of Rubber

Butyl Rubber

Nitrile Rubber

Chloroprene Rubber

Additives to Plastics

Plasticizers	**Brittle –flexible**	**Phthalate, fatty acid**
Lubricant, slip agents	**Molding process**	**Zinc, magnesium sterate, paraffin,PE wax**
Antistatic	**Prevent dust adhesion on surface**	**Quaternary ammonium salts**
Stabilizers	**Improve heat, light resistance**	**Fatty acids, inorganic oxides, organometallics (tin)**
Antioxidants	**Retard oxidative degradation**	**Butylated hydroxy toluene**
Dyes, Pigments	**Color, light protection**	**Titanium dioxide, iron oxides**

Closures

1. **Good Ageing Qualities**
2. **Satisfactory Hardness and Elasticity**
3. **Resistance to Sterilisation Conditions**
4. **Impermeable to Moisture and Air**
5. **Negligible Release of Undesirable Substances**
6. **Negligible Extraction of Injection Ingredients**

Elastomeric Sealants

Elastomer	Physical properties	Water, vapor, gas transmission	Aging & Heat resistance	Oil resistance
Natural latex	+++	-	-	-
Butadiene	+++	-	-	-
Butyl propylene	+	+++	++	++
Ethylene propylene	+	-	+++	++
Styrene/butadiene	++	-	+	++
Nitrite butadiene	++	++	+	++
Polychloro-propene	++	++	++	+++
Silicone	++	-	+++	++

Containers Leaching

- release of components of container into contents
- increased by
  - increased temperature
  - agitation
  - polymer additives

Diffusion Through Polymers

- increased polymer MW ↓
- increased degree of cross-linking ↓
- diluents and plasticizers ↑
- fillers ↓
- increased crystallinity ↓
- increased drug size ↓
- increased hydrophilicity ↓

Moisture

- Sources
  - **Environment during packaging**
  - **product**
  - **transmission through package**
  - **additional internal packaging**
  - **imperfections in the seal are most important source**
- **Avoidance**
- **Select packaging**
  - **ampoules rather than vials**
  - **glass rather than polymer**
- **Calculate moisture**
  - **initial and shelf life**
- **Select dessicant to control adsorption rate**
- **minimise exposure**
  - **control RH during manufacture**
  - **replace air with nitrogen in headspace**

Sorbents and Desiccants

- Activated clays / zeolites
- Silica gel
- Molecular sieve
- Calcium oxide
- Preformed shapes
- Cards with colour indicators
  - not in packages for oral dosage forms
- Sachets in Tyvek
- Canister or cartridges in HDPE
- Cap built into lid

Water Absorbers

- **Silica gel**
- Silicon dioxide
  - pure, porous, amorphous
  - chemically inert, non-toxic, resists attrition
- high capacity > 40% RH
- low capacity < 40% RH
- fair capacity > 32 C
- impregnation with $CoCl_2$: colour change
- most common
- **Activated clay**
- Mined and processed
  - variation in properties
- **Oxide** aluminium, iron and magnesium
- fair absorption capacity at low RH
- poor capacity >32 C
- inexpensive
- specific applications

Sorbents

- Activated carbon
- adsorbs organic compounds
- can be combined with desiccants or oxygen absorbers
- non-toxic
- Ferrous based materials
- absorb oxygen
- irreversible reaction

Tamper Evident Packaging

Ansel p 72-73

Film wrapper	Sealed around product and/or product container; film must be cut or torn to remove product.
Blister/strip pack	Individually sealed dose units; removal requires tearing or breaking individual compartment.
Bubble pack	Product and container sealed in plastic, usually mounted on display card; plastic must be cut or broken open to remove product.
Shrink seal, band	Band or wrapper shrunk by heat or drying to conform to cap; must be torn to open package.
Foil, paper plastic pouch	Sealed individual packet; must be torn to reach product.
Bottle seal	Paper or foil sealed to mouth of container under cap; must be torn or broken to reach product.
Tape seal	Paper or foil sealed over carton flap or bottle cap; must be torn or broken to reach product.
Breakable cap	Plastic or metal tearaway cap over container; must be broken to remove.
Sealed tube	Seal over mouth of tube; must be punctured to reach product.
Sealed carton	Carton flaps sealed; carton cannot be opened without damage.
Aerosol container	Tamper-resistant by design.

Container Labeling

- labels may be intrinsic or applied to the container
- label is designed to meet requirements and must also be submitted to the Regulator
- items that change are date of manufacture and date of expiry
- barcodes are unique for each batch
- numbers of labels are counted before and after batch and must be reconciled.

Container Inspection

- humans have 85% reliability
- machines have 100% reliability

  but no intelligence

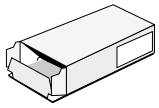
Containers summary

Inner packages

- **Bottles glass or polymeric**
- **tubes polymeric**
- **droppers glass or polymeric**
- **Aerosols: low pressure packed in glass lined with plastic; higher pressure: steel or aluminium coated with plastic; actuator: polyethylene or polypropylene.**
- **Blister pack or foil pack**

Outer packages

- cardboard or paper



Protection

- **Mechanical hazards**
  - **shock or impact**
  - **compression**
  - **vibration**
  - **abrasion**
  - **puncture**
- **Biological hazards**
  - **microbes**
  - **vermin**
  - **humans**
- **Environmental hazards**
  - **moisture**
  - **temperature**
  - **pressure**
  - **light**
  - **gases**
- **Chemical hazards**
  - **adsorption**
  - **absorption and loss**
  - **leaching**
  - **detachment of container**