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CHANGING SCENARIO OF PACKAGING IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

The pharmaceutical packaging market is consistently advancing and has tough annual growth of a minimum of 5% each year within the past few years. The market is now reckoned to be worth over $20 billion a year. Packaging may be a key purchasable, safety and success. Like alternative foodstuff, prescribed drugs packaging got to be in such a way that it'll give speedy packaging, protection, identification, product quality, patient comfort, show and wishes of security. Constant innovations within the prescribed drugs themselves like, blow fill seal (BFS) vials, anti-counterfeit measures, plasma impulse chemical vapor deposition (PICVD) coating technology, snap off ampoules, unit dose vials, two-in-one prefilled vial design, prefilled syringes and child-resistant packs have a direct impact on the packaging. The review details many of the recent pharmaceutical packaging trends that are impacting packaging trade, and offers some predictions for the future.

KEYWORDS: Packaging, Material, Interaction, plastic, glass.

INTRODUCTION

Packaging can be defined as an economical means of providing presentation, protection, identification information, containment, convenience and compliance for a product during storage, carriage, display and until the product is consumed. Packaging must provide protection against climatic conditions biological, physical and chemical hazards and must be economical. The package must ensure adequate stability of the product throughout the shelf life.

The external image of the package must not only compliment product confidence, but provide clear and concise product identification and other features included are:

- Package should provide adequate information related to the contents including legal requirements, route of administration, storage conditions, batch number, expiry date, manufactures name and address and product license number.
- Package should assist in patient compliance.
- Package should preferably have an aesthetically acceptable design.

The primary packaging consist of those packaging components which have a direct contact with the product (i.e. bottle, cap, cap liner, label 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.

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.

Table: 1.

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

The different types of container used as primary packaging for liquid orals are

1. ***Single dose containers*** hold the product that are intended for single use. An example of such a container is the glass ampoule.
2. ***Multi-dose containers*** hold a quantity of the material that will be used as two or more doses. An example of this system is the multiple doses vial or the plastic tablet bottle.
3. ***Well–closed containers*** protect the product from contamination with unwanted foreign materials and form loss of contents during use.
4. ***Airtight containers*** are impermeable to solids, liquids and gases during normal storage and use. If the container is to be opened on more than one occasion it must remain airtight after re closure.

5. ***Sealed container*** such as glass ampoules are closed by fusion of the container material.
6. ***Light – resistant container*** protect the contents from the effect of radiation at a wave length between 290nm and 150nm.

For solid dosage forms

1. ***Tamper – evident containers*** are closed containers fitted with a device that irreversibly indicates if the container has been opened.
2. ***Strip packages*** have at least one sealed pocket of material with each pocket containing a single dose of the product. The package is made of two layers of film or laminate material. The nature and level of protection which is required by the contained product will affect the composition of these layers.
3. ***Blister packages*** are composed of a base layer, with cavities called blisters which contain the pharmaceutical product, and a lid. This lid is sealed to the base layer by heat, pressure or both. They are more rigid than strip packages and are not used for powders or semi-solids. In tropical areas blister packages with an additional aluminium membrane is used which provide greater protection against high humidity.
4. ***Child Resistant Containers***, commonly referred to as CRC's, are designed to prevent the child accessing the potentially hazardous product.

Containers for semi solid and pressurized products

Semi solid dosage forms like ointments, creams etc are packed in metallic collapsible tubes. Plastic containers are also used for the packaging of creams.

Pressurized packages expel the product through a valve. The pressure exerted for the expulsion of the product is an important consideration while selecting the packaging for any products. The main objective of pressurized packaging is that the package must deliver a drug to a specific site for its effective or increased activity in the patient.

FACTORS INFLUENCING THE CHOICE OF PACKAGE

It is essential to have a survey about the market, the distribution system, manufacturing facilities and other considerations before selecting the packaging material.

1. **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.

2. **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 care fully considered during package design and selection.
3. **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 nonexistent.
4. **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.

FUNCTIONS OF PACKAGING

The various functions of packaging are:

1. Protective function
2. Storage function
3. Loading & Transport functions
4. Identification

1. Protective function

Protective function of packaging essentially involves protecting the contents from the environment and vice versa. The inward protective function is intended to ensure full retention of the utility value of the packaged goods. The packaging is thus intended to protect the goods from loss, damage and theft.

In addition packaging must essentially be able to withstand the many different static and dynamic forces to which it is subjected during transport, handling and storage operations. The goods frequently also require protection from climatic conditions, such as temperature, humidity etc. The precipitation and solar radiation may require additional packaging measures in the interior portion of the container.

The exterior protection provided by the packaging must prevent any environmental degradation by the goods. This requirement is of particular significance in the transport of

hazardous materials, with protection of humans being of primary importance. The packaging must furthermore as far as possible prevent any contamination, damage or other negative impact upon the environment and other goods. The interior and exterior protective function primarily places demands upon the strength, resistance and leak proof properties of transport packaging.

2. Storage function

The materials used for packaging should be stored properly so as to preserve the quality of the material both before packaging and once the package contents have been used.

3. Loading and transport functions

Packaging has a crucial impact on the efficiency of transport, handling and storage of goods. Packaging should therefore be deigned to be easily handled and to permit space-saving storage and stowage. The shape and strength of packages should be such that they may not only be stowed side by side leaving virtually no voids but may also stowed safely one above the other.

The most efficient method of handling general cargo is to make up cargo units. Packaging should thus always facilitate the formation of cargo units; package dimensions and the masses to be accommodated should be possibly tailored to the dimensions and load- carrying capacity of standard pallets and containers.

Handling of the package is done entirely or partially by manual method when the packages are easy to pick up and are of a suitably low mass. Mechanical handling is well suited during the package of heavy goods. The loading and transport function depends upon the external shape of the package, the mass of the goods accommodated inside and upon the convenient use of packaging aids.

4. Identification

The packaging should give clear identification of the product at all stages. The life of the patient may depend upon rapid and correct identification in emergencies. Packaging also serves as a mean to identify the manufacturer of the product. The manufacturer must consider the packaging requirement for the usage of product in different localities.

PROPERTIES OF THE PACKAGING MATERIAL

To afford the necessary protection, the materials from which the container is to be made must show certain basic properties which can be divided into four groups.

1) Mechanical Properties

The materials used should possess sufficient mechanical strength to withstand while handling, filling, closing and processing. Typical care is needed during transport, storage and also at the time of usage by the consumer especially in case of glass containers. A glass container will have greater strength if all corners are rounded.

2) Physical properties

- The material should be impervious to any possible contaminants, for example, solids, liquids, gases, vapors or microorganisms.
- The container must be able to withstand heat if the processing includes sterilization.
- The surface must be capable of clear labeling, often difficult, for example, with plastics.
- The packaging must have a suitable size, thus, rubber may presents problems if it perishes.
- The material must protect from light if necessary, that is, it must be ultraviolet absorbent.
- The container must not absorb substances from the products; e.g. absorption of water from creams in to cardboard box.

3) Chemical Properties

- The container and the closure should not react together, either alone or in the presence of the product. This can occur with certain combination of dissimilar materials.
- The product should not react with the container or closure, as might happen if alkaline substances are placed in aluminium containers.
- Substances must not be extracted from the product, such as the loss of bactericides from injection solution to rubber.
- The container or closure must not yield substances to the product; for example, alkali from glass, plasticizers from plastics etc.

4) Biological properties

The material of the container must be able to withstand attack by insects if this hazard is likely to be encountered. The packing should not support mould growth. The risk is greatest

with cellulosic substance and if the use of such materials is unavoidable, the attack may be minimized by impregnation.

HAZARDS ENCOUNTERED BY THE PACKAGE

Hazards encountered by the package can be divided into three main groups—mechanical hazards, climatic or environmental hazards and biological hazards. The only exception is theft, which can be a serious risk with drugs and may demand special protection in certain cases.

1) Mechanical Hazards

a) Shock or impact damage

Damage due to shock is usually caused by rough handling, during transport etc. Cushioning can be provided and a warning label may be useful. Restriction of movement and more careful handling should be made.

b) Compression

Fragile items may be broken, or collapsible articles crushed by compression, the usual procedure then being to protect with a rigid outer package. Top pressure or loading can distort inside. The crushing of a carton can make a product un- sealable even though no damage has occurred to the contents. This is more likely to occur during stocking in the ware house or during transport where vibration adds a further hazard. Compression can also occur in other situations like capping on a production line, when being carried home by the user etc.

c) Vibration

Vibration consists of two variables-frequency and amplitude. Considerable vibration may occur during transport, especially with exported items. Damage may be external, such as the 'scuffing' of labels, but some products may be affected like the cracking of emulsions, abrasion of tablets, or segregation of mixed powders. Some times screw caps may be loosen or labels or decorations may abrade etc.

d) Abrasion

Although abrasion results form both regular and irregular forms of vibration, it is listed separately as the visual appearance of the product or package can be affected. eg: rectangular bottle in a carton will move up and down and from side to side. A round bottle in the same circumstances will suffer from an additional possibility of rotation.

2) Climatic or environmental hazards

Environmental conditions encountered by the package are likely to vary considerably, especially in articles for export to the tropical areas. In general, it is extremes of conditions that give rise to problems, and this is especially true of fluctuating conditions.

a) Temperature

Extreme conditions may cause deterioration, low temperatures leading to aqueous solutions freezing and, hence, to fracture of containers. High temperatures increase diffusion coefficients, accelerating the entry of water vapor into hygroscopic products and the loss of volatile components. In addition, high, temperatures increase reaction rates and product breakdowns either by hydrolysis or oxidation. High temperature coupled with a high relative humidity will produce a slower effect if the temperature is lowered sufficiently to reach dew point. Contamination from liquid moisture can encourage mold and bacterial growth.

b) Moisture

Moisture as liquid or water vapor may cause physical changes (e.g. color fading, softening, hardening etc) or chemical changes (hydrolysis, oxidation, effervescence etc.). Although liquid moisture may cause obvious damage, water vapor may penetrate into a package, leading to hydrolysis, without visual changes. It is essential to check the water vapor permeability of materials to be used for packaging moisture-sensitive products; for example, plastics show considerable variation in this property. It may also act as a carrier for other contaminants like molds and fungi.

c) Pressure

Decrease in pressure, as in mountainous regions or during flight in non-pressurized transport aircraft, may cause thin containers to burst or strip packs to inflate.

d) Atmospheric Gases

Gases from the atmosphere may diffuse into the package, leading to deterioration. Thus, oxygen will encourage oxidation, while carbon dioxide can cause a p^H shift (un buffered solution in plastic bottle particularly Low Density Poly Ethylene (LDPE), which is relatively permeable to carbon dioxide) or lead to precipitation of some products (barbiturates from solutions of their sodium salts). Permeation of the common gases through plastic is typically in the ratio of 1:4:20 for nitrogen, Oxygen and Carbon dioxide respectively, nitrogen being more permeable. Odorous gases or volatile ingredients associated with perfumes, flavors and product formulation may also pass into or out of a package. If a volatile ingredient is lost from a flavor, an unpleasant odor or taste may result.

e) Light

Light consist of wavelengths from the UV zones through the visible to infrared. A number of deteriorations are due to photochemical reactions particularly affected by the ultra-violet band of the spectrum. Such changes may not always be visible. Printed or deteriorated packaging materials may also suffer from discoloration (white may go yellow, deeper colors may fade) and this may be seen as implying a change in the product efficacy or strength. Although light can be excluded by using selected material, tin plate, soil etc. opacity and/or color may reduce penetration or filter out selected wavelength. The additional use of UV absorbers in plastics may also restrict light rays entering the packed it should also be noted that many products are protected by a carton, outer etc. Alternatively, an opaque outer packaging may be used, with a warming that the advantage that the latter may be transparent, permitting the contents to be inspected.

f) Solid Airborne Contamination (Particulars)

Particulars matters present in the atmosphere will make the containers dirty during transport or storage. This can be prevented by outer wrappers or by anti static agents.

3) Biological hazards

a) Microbiological

The packaging materials must be reasonably clean initially and when put together to form a finished package and restrict any further contamination as much as possible. In the case of sterile products the package and its closure must maintain a 100% effective seal against microbiological contaminants like bacteria, moulds and yeasts. Growth of yeasts is critical with sugar based products as fermentation may occur. Moulds will also grow on cellulose based materials like paper if these are kept under humid conditions. Care should be taken in order to avoid fluctuation in temperature.

b) Other forms of infestation

Other forms of infestation that can contaminate pharmaceutical products include attack by insects, termites, vermin, rodents or any other bird or animal. Contaminating source. Although this is more likely to happen under poor controlled conditions & hygiene and housekeeping, such infestation can still occasionally cause problems.

***c)* Pilferage and adultration risks**

Pilferage being a human failure is another biological hazard. The example of the Tylenol poisoning in 1982 has placed greater emphasis on the need for tamper-resistant packaging prior to this, various seals were used to indicate whether any product had been removed or

replaced, rather than as a means of increasing and maintaining user confidence in the product and package.

4) Chemical Hazards

The main risk of chemical hazard is due to interaction or in compatibility between the product and package. Compatibility investigations must basically cover any exchange that can occur between the product and the package and vice versa. These may be associated with interaction or contamination, covering migration, absorption, adsorption, extraction, corrosion, etc. where by ingredients may either be lost or gained. Such exchange may be identifiable as organoleptic changes, increase in toxicity/irritancy degradation, loss or gain of microbial effectiveness, precipitation, turbidity, color change, P^H shift etc. These external influences may catalyze, induce or even nullify chemical changes.

PACKAGING COMPONENTS

The materials selected should have the following characteristics.

They must protect the preparation form environmental conditions.

- They must not be reactive with the product.
- They must note impart taste or odor to the product.
- They must be nontoxic.
- They must be Food and Drug Administration approved.
- They must meet applicable tamper – resistance requirements.
- They must be adaptable to commonly employed high speed packaging equipments.

Packaging Materials Used In Different Formulations

1) Paper and Board

The use of paperboard materials (cellulose fiber) remains a significant part of pharmaceutical packaging in spite of the facts that paper is rarely used on its own for a primary package. Cartons are used for a high percentage of pharmaceutical products for a number of reasons, increasing display area, providing better display of stock items and the collating of leaflets which would otherwise be difficult to attach to many containers. Cartons also provide physical protection especially to items such as metal collapsible tubes. Carton therefore tend to be a traditional of pharmaceutical packaging.

Regenerated cellulose film (trade names cellophane and rayophane) are still used as an over wrapping material either for individual cartons or to collate a number of cartons. It is being

substantially replaced by orientated polypropylene film. Although paper, even when waxed, has relatively poor protective properties against moisture, both paper and board (ointment, pill and tablets boxes) were once used widely for primary packages, particularly for dispensing operations.

2) Rubber Based Components

Rubber components may be made from either natural or synthetic sources. Natural rubber has got good resealing (multi-dose injection), fragmentation and coring(description for the means by which particles are created when a needle is passed through a rubber) when compared to synthetic rubber; but is poor in respect to ageing and chances of moisture and gas permeation and the absorption of preservative systems is more. Sterilization by multiple autoclaving is also not possible. Synthetic rubbers tend to reverse all of these properties and some formulations actually contain natural rubber in order to improve re sealability, fragmentation and coring. Most rubber formulation are relatively complex and may contain one or more of the vulcanizing agents, accelerators, fillers, activators, pigments, antioxidants, lubricants, softeners or waxes. The main types of rubber used for pharmaceutical products include natural rubber, neoprene, nitrile, butyl, chlorobutyl, bromobutyl and silicone. Of these silicone is the most expensive and although the most inert, is readily permeable to moisture, gases and absorbent to certain preservatives. Rubber components are likely to contain more additives than plastics. Hence product-package interactions should be properly tested before they are used for injectable or intravenous type products. Rubber gaskets are also sound in aerosols and metered -dose pump systems.

3) Tamper-Resistant Packaging

The requirement for tamper –resistant packaging is now one of the major consideration in the development of packaging for pharmaceutical products As defined by the FDA "a tamper –resistant package is one having an indicator or barrier to entry which, if breached or trussing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred tamper –resistant packaging may involve immediate –container /closure systems or secondary –container /carton systems or any combination thereof intended to provide a visual indication of package integrity when handled in a reasonable manner during manufacture, distribution, and retail display ".

The following package configuration have been identified by the FDA as examples of packaging systems that are capable of meeting the requirements of tamper-resistant packaging as defined by FDA regulation

1. Film wrappers
2. Blister package
3. Strip package
4. Bubble pack
5. Shrink seal and bands
6. Foil paper or plastic pouches
7. Bottle seals
8. Tape seals
9. Breakable caps
10. Sealed tubes
11. Aerosol containers
12. Sealed cartons

1. Film wrapper

Film wrapping has been used extensively over the years for products requiring package integrity or environmental protection. Film wrapping can be accomplished in several ways and varies in configuration with packaging equipment.

Film wrapping machines can be generally categorized into the following types:

- **End-folded wrapper**

The end –folder wrapper is formed by pushing the product into a sheet of over wrapping film, which forms the film around the product and folds the edges in a gift-wrap fashion. The folded areas are sealed by pressing against a heated bar. Because of the overlapping folding sequence of the seals, the film used must be heat –sealable on both surfaces. Materials commonly used for this application are cellophane and polypropylene. Cellophane, which is regenerated cellulose, is not inherently heat-sealable but requires a heat-seal coating to impart heat-sealing characteristics to the film. This is usually accomplished by coating the cellophane with either polyvinylidene chloride (PVDC) or nitrocellulose. The PVDC provides a durable moisture barrier, PVDC coated cellophane is often used for the over wrapping of products that are sensitive to moisture. To be tamper-resistant, the over wrap must be well sealed and must be printed or uniquely decorated. If the print of the carton being

over wrapped is coated with a heat-sensitive varnish, it causes the over wrap to bond permanently to the paperboard carton during the sealing of the over wrap.

- **Fin seal wrapper**

Unlike the end folded wrapper configuration, fin seal packaging dose not require the product to act as a bearing surface against which the over wrap is sealed. The seal are formed by crimping the film together and sealing together the two inside surface of the film, producing a "fin" seal Since the seals are formed by compressing the material between two heater bars rather than sealing against the package. When more consistent and greater sealing pressure is applied, better seal integrity can be accomplished .For this reason, fin sealing has primarily been used when protective packaging is critical. Since the surface of the heat seal dose not come in contact with the heated sealing bars on the packaging equipment, much more tenacious heat sealants such as polyethylene can be used. With good seal integrity, the over wrap can be removed or opened only by tearing the wrapper.

- **Shrink Wrapper**

Film over wrapping can also be accomplished with the use of a shrink wrapper. The shrink wrap concept involves the packaging of a product in a thermoplastic film that been stretched and oriented during its manufacture and that has the property of reverting back to its un-stretched dimension once the molecular structure is "unfrozen" by the application of heat. The shrink wrap concept has a diversity of uses in packaging, one of which is its use as an over wrap. In this case, the shrink film is usually used in roll form, with the center folder in the direction of winding. As the film unwinds on the over wrapping machine, a pocket is formed in the center fold of the sheet, into which the product is inserted. An L-shaped sealer seals the remainder of the over wrap and trims off the excess film. The loosely wrapped product is then moved through a heated tunnel, which shrink the over wrap into a tightly wrapped unit The material commonly used for this application are heat –shrinkable grades of polypropylene, polyethylene, and poly vinyl chloride. Since the various heat-shrinkable grades of film have different physical characteristic such as tear and tensile strength, puncture resistance, and shrinking forces, selection of the particular material used must be based upon specific product consideration so that the shrink wrap provides suitable integrity without crushing or damage the product. The major advantages of this type of wrapper are the flexibility and low cost of the packaging equipment required.

2) Blister Package

When one thinks of unit dose in pharmaceutical packaging, the package that invariably comes to mind is the blister package. This packaging mode has been used extensively for pharmaceutical packaging for several good reasons. It is a packaging configuration capable of providing excellent environmental protection, coupled with an esthetically pleasing and efficacious appearance. It also provides user functionality in terms of convenience, child resistance, and now, tamper resistance.

The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic into 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. For a push-through type of blister, the backing material is usually heat-seal-coated aluminum foil. The coating on the foil must be compatible with the blister material to ensure satisfactory sealing, both for product protection and for tamper resistance. Peelable backing materials have been used to meet the requirements of child-resistant packaging. This type of backing must have a degree of puncture resistance to prevent a child from pushing the product through the lidding and must also have sufficient tensile strength to allow the lidding to be pulled away from the blister even when the lidding is strongly adhered to it. To accomplish this, a material such as polyester or paper is used as a component of the backing lamination. Foil is generally used as a component of the backing lamination if barrier protection is a critical requirement; however, metallized polyester is replacing foil for some barrier applications. A peelable sealant compatible with the heat-seal coating on the blister is also required since the degree of difficulty of opening is a critical parameter for child-resistant packaging. The use of peelable backing materials for blister packaging must be carefully evaluated to ensure that peelstrengths are sufficient to meet tamper-resistance objectives.

Materials commonly used for the thermo-formable blister are poly vinyl chloride (PVC), PVC/polyethylene combinations, polystyrene, and polypropylene. For commercial reasons and because of certain machine performance characteristics, the blisters on most unit dose packages are made of polyvinyl chloride. For added moisture protection, polyvinylidene chloride (saran) or polychlorotrifluoroethylene (Aclar) films may be laminated to PVC. The

moisture barrier of PVC/Aclar is superior to that of saran-coated PVC, especially under prolonged and extremely humid storage conditions.

3) Strip Package

A strip package is a form of unit dose packaging that is commonly used for the packaging of tablets and capsules. A strip package is formed by feeding two webs of a heat-sealable flexible film through either a heated crimping roller or a heated reciprocating plate. The product is dropped into the pocket formed prior to forming the final set of seals. A continuous strip of packets is formed, generally several packets wide depending on the packaging machine's limitations. The strip of packets is cut to the desired number of packets in length. The strips formed are usually collated and packaged into a folding carton. The product sealed between the two sheets of film usually has a seal around each tablet, with perforations usually separating adjacent packets. The seals can be in a simple rectangular or "picture-frame" format or can be contoured to the shape of the product. Since the sealing is usually accomplished between pressure rollers, a high degree of seal integrity is possible. The use of high-barrier materials such as foil laminations or saran-coated films, in conjunction with the excellent seal formation, makes this packaging mode appropriate for the packaging of moisture-sensitive products.

Different packaging materials are used for strip packaging based on their properties. Few examples are cited below:

For high-barrier applications, a paper/polyethylene/foil/polyethylene lamination is commonly used. When the visibility of the product is important, heat-sealable cellophane or heat-sealable polyester can be used. In some cases the the material used on either sides of the strip package varies and the choice of material used depends on both the product and the equipment.

4) Bubble Pack

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 generally accomplished by heat-softening the plastic film and vacuum-drawing a pocket into the film in a manner similar to the formation of a blister in a blister package. The product is dropped into the pocket, which is then sealed to a rigid material such as heat-seal-coated paperboard. If a heat-shrinkable material is used, the

package is passed through a heated tunnel, which shrinks the film into a bubble or skin over the product, firmly attaching it to the backing card.

5) Shrink Banding

The shrink band concept makes use of the heat-shrinking characteristics of a stretch-oriented polymer, usually PVC. The heat-shrinkable 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. The heat-shrinkable material is supplied to the bottler as a printed, collapsed tube, either pre-cut to a specified length or in roll form for an automated operation. The proper length of PVC tubing is slid over the capped bottle far enough to engage both the cap and neck ring of the bottle .The bottle is then moved through a heat tunnel, which shrinks the tubing tightly around the cap and bottle, preventing the disengagement of the cap without destroying the shrink band. For ease of opening, the shrink bands can be supplied with tear perforations.

6) Foil, Paper, or Plastic Pouches

The flexible pouch is a 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, and sealing (f/f/s) equipment.

In the vertical forming, filling, and sealing (f/f/s) operation, a web of film is drawn over a metal collar and around a vertical filling tube, through which the product is dropped into the formed package. The metal filling tube also acts as a mandrel, which controls the circumference of the pouch and against which the longitudinal seal is made. The formation of this seal, which can be either a fin seal or an overlap seal, converts the packaging film into a continuous tube of film. Reciprocating sealers, orthogonal to the longitudinal seal, crimp off the bottom of the tube, creating the bottom seal of the package. The product drops through the forming tube into the formed package. The reciprocation sealer moves up the film tube a distance equal to the length of the package and forms the top and final seal of the package.

The top seal of the package becomes the bottom seal of the next package and the process repeats itself. Since vertical f/f/s machines are gravity-fed, they are primarily used for liquid, powder, and granular products.

The horizontal forming, filling, and sealing (f/f/s) system is generally used for products of smaller volume, which are more amenable to the flatter format of the packages. In this system, the web of film is folded upon itself rather than around a tube. As the folded film is fed horizontally through the equipment, a reciprocating platen creates pockets in the film by making vertical separation seals. The product is then placed into each pocket and the final top seal is made. Packages formed on horizontal f/f/s equipment typically have a three-sided perimeter seal, but other variations are possible, depending on the type of equipment used. For moisture- and oxygen-sensitive products, foil is commonly used as part of the film lamination. Now a days foil is replaced by metallized polyester which is used in the lamination for high barrier application and include paper/polyethylene/foil/polyethylene and polyester/polyethylene/foil/polyethylene. They offer some advantages that they are of lower cost, excellent appearance, and flexural endurance.

7) Bottle Seals

A bottle may be made tamper-resister 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 irreparably destroying the seal. Various inner seal compositions may be used, but the structures most frequently encountered are glassine and foil laminations. Typically, glassine liners are two-ply laminations using two sheets of glassine paper bonded together with wax or adhesive. The inner seals are inserted into the bottle cap and held in place over the permanent cap liner by either by applying friction or by the a slight application of wax which temporarily adheres the seal to the permanent cap liner. If glue-mounted inner seals are to be used, glue is applied to the rim of the bottle prior to the capping operation. The application of the cap forces the inner seal into contact with the glued bottle rim and maintains pressure during glue curing and until the cap is removed. When the bottle cap is removed, the inner seal is left securely anchored to the bottle rim.

Pressure-sensitive inner seals can also be used. The pressure-sensitive adhesive is coated on the surface of the inner seal as an encapsulated adhesive. During the capping operation, the torque pressure ruptures the encapsulated adhesive, which then bonds the inner seal to the rim of the bottle. One type of pressure-sensitive inner seal is constructed of thin-gauge styrene foam inner seal material coated on one side with a specially formulated torque-activated adhesive. The adhesive has minimal surface tack, but when applied with a properly torqued cap, it provides excellent adhesion to both glass and plastic bottles.

A third method of application uses a heat-sensitive adhesive that is activated by high-frequency induction. This type of application requires the use of aluminum foil as part of the inner seal composition. Once the cap is applied, the bottle is passed under an induction coil, which induces high-frequency resonation in the foil. The frictional heat that is generated activates the heat-seal coating and bonds the liner to the bottle. This type of seal can only be used with plastic caps since metal caps would interfere with the induction sealing of the inner seal. To meet the tamper-resistant criteria, the inner seals must be printed or decorated with a unique design. The seal must also be bonded sufficiently to ensure that its removal would result in destruction of the seal.

8) Tape Seals

Tape sealing 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 a high-density lightweight paper with poor tear strength. Labels made of self-destructing paper are available; these cannot survive any attempt at removal once they have been applied. To reduce further the possibility of removing the label intact, perforation or partial slitting of the paper can be made prior to application so that the label tears readily along those weak points if any attempt is made to remove it.

9) Breakable Caps

Breakable closures come in many different designs. The roll-on cap design used in the past for carbonated beverages uses an aluminum shell, which is placed over the bottle -neck during the 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 the 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 a 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 the 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.

10) Sealed Tubes

Collapsible tubes used for packaging are constructed of metal, plastic, or a lamination of foil, paper, and plastic. Metal tubes are still used for those products that require the high degree of

barrier protection afforded by metal. Most of these are made of aluminum and are usually coated to eliminate compatibility problems between product and package. Puncture inserts, which are usually made of aluminium are used to seal the tube opening for tamper resistance. These inserts have to be punctured and pried out to gain access to the product. Extruded plastic tubes are widely used for those products that are compatible with the limited barrier characteristics of plastic. These tubes are usually constructed of polypropylene or polyethylene. For high-barrier packaging, metal or laminated tubes are used. Laminated tubes are constructed of a multilayer lamination made of foil, paper, and plastic specifically tailored to the product requirements. The lamination is used for the body of the tube with the head injection molded onto the tube. Since the head is injection-molded, any number of designs are available that must be cut or broken to gain access to the product. These seal end designs are usually molded of low-density polyethylene. The tubes are filled from the other end and are sealed either by crimping the end in the case of metal tubes, or by induction sealing in the case of plastic or laminated tubes.

11) Aerosol Containers

The aerosol container used for pharmaceutical products is usually made of aluminum compounds. 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 tubing, 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 dispensed with each spray. The design of the aerosol package makes it inherently tamper-resistant.

12) Sealed Cartons

Folding paperboard cartons have been used as a secondary package for Over The Counter(OTC) products for many years. The popularity of this packaging mode is based on both functional and marketing considerations. With the advent of mass marketing of Over The Counter(OTC) products in the self-service sections of larger stores, shelf presence and product stack-ability became a dominant consideration in the package design. Labeling requirements in many cases exceeded the limited copy area provided by the label on the primary container and consequently required additional copy area to be provided as either

inserts or carton panels. All of these considerations were addressed with the use of a folding carton to contain the primary package.

The closure of folding cartons can be accomplished in a number of ways. The most prevalent method has been the use of the "tuck end" design. The tuck end design feature allow the ends of the carton to be held closed by the physical engagement of the side tabs at the open end of the carton, with the slits placed in the carton tuck or lid. This design feature, which has been prevalent in the folding carton industry because of its functionality and compatibility with high speed packaging equipment. It is no longer considered an acceptable closure mechanism for Over The Counter (OTC) products. If tuck end cartons are to be used, they must be augmented with some other form of tamper-resistant packaging such as film over-wrapping, tape sealing or glue sealing the carton. Seal end cartons differ from tuck end cartons in that rather than using the mechanical interlocking design of the tuck end to close the carton, externally applied glue or hot melt is used to provide carton sealing.

GLASS CONTAINERS

Glass is commonly used in pharmaceutical packaging because it possesses superior protective qualities.

Advantages

- Economical
- Readily available container of variety of sizes and shapes
- Impermeability
- Strength and rigidity
- Has FDA clearance
- Does not deteriorate with age
- Easy to clean
- Effective closure and resolves are applicable.
- Colored glass, especially amber, can give protection against light when it is required.

Disadvantages

- Fragility
- Heavy weight

Composition of Glass

Glass is composed principally of silica with varying amount of metal oxides, soda-ash, limestone, and cullet. The sand is almost pure silica, the soda-ash is sodium carbonate, and the limestone, calcium carbonate. Cullet is broken glass that is mixed with the batch and acts as a fusion agent for the entire mixture. The composition of glass varies and is usually adjusted for specific purposes. The most common cations found in pharmaceutical glassware are silicon, aluminum, boron, sodium, potassium, calcium, magnesium, zinc, and barium. The only anion of consequence is oxygen. Many useful properties of glass are affected by the kind of elements it contains. Reduction in the proportion of sodium ions makes glass chemically resistant; however, without sodium or other alkalies, glass is difficult to melt and is expensive. Boron oxide is incorporated mainly to aid in the melting process through reduction of the temperature required.

Lead in small traces gives clarity and brilliance, but produces a relatively soft grade of glass. Alumina (aluminum oxide), however, is often used to increase the hardness and durability and to increase resistance to chemical action.

Manufacture of Glass

Four basic processes are used in the production of glass: blowing, drawing, pressing, and casting. *Blowing* uses compressed air to form the molten glass in the cavity of a metal mold. Most commercial bottles and jars are produced on automatic equipment by this method. In *drawing*, molten glass is pulled through dies or rollers that shape the soft glass. Rods, tubes, sheet glass, and other items of uniform diameter are usually produced commercially by drawing. Ampoules, cartridges, and vials drawm from tubing have a thinner, more uniform wall thickness, with less distortion than blow-molded containers. In *pressing*, mechanical force is used to press the molten glass against the side of a mold. *Casting* uses gravity or centrifugal force to initiate the formation of molten glass in the cavity.

1) Colored Glass-Light Protection

Glass containers for drugs are generally available in clear flint or amber color. For decorative purposes, special colors such as blue, emerald green, and opal may be obtained from the glass manufacturer. Only amber glass and red glass are effective in protecting the contents of a bottle from the effects of sunlight by screening out harmful ultraviolet rays. The USP specifications for light-resistant containers require the glass to provide protection against 2900 to 4500 Angstroms of light. Amber glass meets these specifications, but the iron oxide

added to produce this color could leach into the product. Therefore, if the product contains ingredients subject to iron-catalyzed chemical reactions, amber glass should not be used. Manganese oxide can also be used for amber glasses.

2) Glass for Drugs

The USP and NF describe the various types of glass and provide the *powdered glass* and *water attack* tests for evaluating the chemical resistance of glass. The test results are measures of the amount of alkalinity leached from the glass by purified water under controlled elevated temperature conditions. The powdered glass test is performed on crushed glass of a specific size, and the water attack test is conducted on whole containers. The water attack test is used only with type II glass that has been exposed to sulfur dioxide fumes under controlled conditions.

Type I- Borosilicate Glass

Borosilicate Glass is a highly resistant glass. In this type of glass a substantial part of the alkali and earth cations are replaced by boron and/or aluminum and zinc. It is more chemically inert than the soda-lime glass, which contains either none or an insignificant amount of these cations. Although glass is considered to be a virtually inert material and is used to contain strong acids and alkalies as well as all types of solvents, it has a definite and measurable chemical reaction with some substances, notably water. The sodium is loosely combined with the silicon and is leached from the surface of the glass by water. Distilled water stored for one year in flint type III glass (to be described) picks up 10 to 15 parts per million (ppm) of sodium hydroxide along with traces of other ingredients of the glass. The addition of approximately 6% boron to form type I borosilicate glass reduces the leaching action, so that only 0.5 ppm is dissolved in a year.

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," and in its early stages, it gives the appearance of fine crystals on the glass. At this stage, these salts can be washed off with water or acid. 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. The treatment offered by several glass manufacturers exposes the glass to

an atmosphere containing water vapor and acidic gases, particularly sulfur dioxide at an elevated temperature. This results in a reaction between the gases and some of the surface alkali, rendering the surface fairly resistant, for a period of time, 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. Sulfur treatment neutralizes the alkaline oxides on the surface, thereby rendering the glass more chemically resistant.

Type III-Regular Soda-Lime Glass

Containers are untreated and made of commercial soda-lime glass of average or better-than-aver-age chemical resistance.

Type NP-General-Purpose Soda-Lime Glass

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

Other types of glass are

Neutral glass

Borosilicate glasses have two major disadvantages, they are expensive and difficult to melt and mould. So manufactures have produced another grade of glass (described as neutral) which are softer and more easily manipulated than borosilicate glass. Neutral glass have good resistance to autoclaving, weathering and is also resistant to solution of p^H up to about 8. Neutral glass has a higher melting temperature ($1750\ ^0C$) and a narrower working temperature range.

Lead free glass

Lead monoxide is used in the manufacture of certain types of glasses, but as lead is a cumulative poison, lead free containers are desirable for pharmaceutical preparation, particularly those intended for oral liquids.

Sulfured containers

An alternative approach in the search for cheaper containers particularly for large volume injections is surface treatment. For example, by a process known as sulfuring. The containers are exposed to moist sulfur dioxide at above 500^0C. The acid gas neutralizes the sulfate which can be removed by washing and expose to a tough silica rich surface.

Silicon treated containers

Silicones are polymers composed of long chains of alternating oxygen and silicon atoms with organic attached to the later. Silicones are chemically related to glass and shows good resistance to heat and oxidation, chemical inertness, freedom from color, odor and toxicity. Organic groups in silicone molecules confers valuable properties of water repellency. This characteristic can be given to container by treatment with a suitable silicone. The main advantage of silicone treated injection containers is that they are not wetted by aqueous solution or suspension which there for do not cling to the sides.

Ampoules

Ampoules are thin-walled glass containers, which after filling, are sealed by either tip sealing or pull sealing. The contents are withdrawn after rupture of the glass, or a single occasion only. These are great packaging for a variety of drugs. The filed – in product is in contact with glass only and the packaging is 100% tamper proof. The break system OPC(one –point cut) or the color break ring offer consistent breaking force. There are wide variety of ampoule types from 0.5 to 50ml. Up to 3 color rings can be placed the stem or body for identification purpose. Printed ampoules with heavy metal free colors are available. Some of them are:

- Type B straight –stem
- Type C funnel –tip
- Type D closed
- Double tip (1-25 ml)
- Fine tip (1-25 ml)

Bottles, vials and syringes

These are more or less thick walled containers with closures of glass or of material other than glass such as plastic materials or elastomers. The contents may be removed in several proportions on one of or more occasions.

Containers for Blood and Blood Components

These are cylindrical more or less thick walled containers of various capacities and of colorles and transparent neutral glass. Colorless glass is lightly transparent in the visible spectrum and colored glass is obtained by the addition of small amounts of metal oxides, chosen according to the desired spectral absorbance. Colored glass are not used for parenteral products. Colorless or colored glass can be used for other pharmaceutical products. If product is light sensitive, the transparency should not be effected so that the inside content can be

visualized. The inner surface of the glass containers may be specially treated to improve hydrolytic resistance.

Test for glass containers

A) Test for surface hydrolytic resistance

Surface hydrolytic resistance test is conducted on unused glass containers. The number of containers to be examined and the volume of the test humid necessary for final determination are indicated in the following table (2).

Table (2).

Nominal capacity of container	Number of containers to be used	Volume of test solution to be used for titration ml
3 or less	At least 10	25.0
3 to 30	At least 5	50.0
More than 30	At least3	100.0

Initially each container is rinsed three times carefully with carbon dioxide free water. Then the container is allowed to drain and it is filled with the carbon dioxide free water to the required volume. If vials and bottle are used they are covered with neutral glass dishes or aluminum foil which is previously rinsed with carbon dioxide free water. If ampoules are used, they are sealed by heat fusion. The containers are then placed on the tray of the autoclave a containing a quantity of water in such a way that the tray remains clear and temperature is maintained between 100^{o}C to 120^{o} C over 20minutes. Then the temperature is adjusted between 120^{o}-122^{0}C for 60 minutes and finally the temperature is lowered from 120^{o}C for 40 minutes. Remove the containers from the autoclave once the pressure reaches the atmospheric pressure and cool under running tap water Combine the liquids obtained from the containers being examined. The following titration should be carried out within 1 hour after removing the container from the autoclave. Introduce the prescribed volume of liquid in to a conical flask. Add 0.05ml of methyl red solution for each 20ml liquid. Titrate with 0.01M hydrochloric acid taking as the end point the color obtained by repeating the operation using the same volumes of carbon dioxide free water. The result is not greater than the volume state in table (3).

Table 3.

Capacity of container	Volume of 0.01M hydrochloric acid VS per 100 ml of test solution	
	Type 1 or II glass ml	Type III glass ml
Not more than 1	3.0	20.0
More than 1 but not more than 2	1.8	17.6
More than 2 but not more than 5	1.3	13.2
More than 5 but not more than 10	1.0	10.2
More than 10 but not more than 20	0.80	8.1
More than 20 but not more than 50	0.60	6.1
More than 50 but not more than 100	0.50	4.8
More than 100 but not more than 200	0.40	3.8
More than 200 but not more than 500	0.30	2.9
More than 500	0.20	2.2

B). Test for hydrolytic resistance of powdered glass

The Containers to be tested are initially rinsed with water and dried in hot air oven. At least three containers are taken and broken with a hammer to get coarse fragments of about 100g size of the largest fragment should not be greater than 25mm. Transfer a part of the sample to a mortar and insert the pestle and strike heavily once with the hammer. Transfer the contents of the mortar to the coarsest sieve. Repeat the operation sufficient number of times until all the fragment have been transferred to the sieve. The glass is sifted and the portion retained by the 710□m and 423 □m sieve are taken and are further fractured. The operation is respected until 20g of glass is retained by the 710□m sieve. Rejected this portion and the portion that passes through 250□m sieve. Shake the nest of sieve manually or mechanically for 5 minutes. Glass grains that passes through 425□m sieve is taken metal particles are removed by suspending the glass grains in acetone the supernatant liquid is decanted the operation is repeated five times glass grains are speeded on an evaporating dish and allow the acetone to evaporating by drying in an oven at 110^{o}C for 20minutes and allow to cool.

20g of the glass grains to treated is introduced into a 250ml conical flask add 100ml of carbon dioxide free water and weigh In the second flask 100ml carbon dioxide free water

serve as blank and weigh. Close the two flasks with neutral glass dish or aluminum foil rinsed with carbon dioxide free water. The flask is then placed in on auto clave and maintain the temperature at 121^{o}C for 30minutes and carry out the operations similar to those described in Test A for surface hydrolytic resistance. After cooling remove the closure, wipe the flask and adjust the original weight by adding carbon dioxide free water. Transfer 50ml (corresponding to 10g of glass grains) of the clear supernatant liquid into a conical flask. 50ml of water is taken in other flask which is used as blank 0.1ml methyl red solution is added as indicator and titrated with 0.001M hydrochloric acid until the color of the liquid is same as that obtained with blank. Subs tract the value of the blank and express the result in millilitres of hydrochloric acid consumed per 10g of glass. Type I glass containers require not more than 2.0ml, Type II or III requires not more than 17.0ml and Type IV glass containers requires not more than 30.0ml of 0.001M hydrochloric acid.

C) Test for hydrolytic resistance of the etched surface of the container

The number of the containers to be tested and the volume of the test liquid required in as shown in Table (2).

Rinse the containers twice with carbon dioxide -free water, fill completely with a mixture of I volume of hydrofluoric acid and 9 volumes of hydrochloric and and allow to stand for 10 minutes. Empty the containers and rinse carefully five times with carbon dioxide -free water. Immediately before the test, rinse once again with carbon dioxide-free water. The containers prepared is subjected to the same autoclaving and titration procedure as that described in Test A for surface hydrolytic resistance.

PLASTIC CONTAINERS

Plastics in packaging have proved useful for a number of reasons, including the ease with which they can be formed, their high quality, and the freedom of design to which they lend themselves. Plastic containers are extremely resistant to breakage and thus offer safety to consumers along with reduction of breakage losses at all levels of distribution and use. Plastic containers for pharmaceutical products are primarily made from the following polymers: polyethylene, polypropylene, polyvinyl chloride, polystyrene, and to a lesser extent, polymethyl methacrylate, polyethylene terephthalate, polytrifluoroethylene, the amino formaldehydes, and polyamides. Plastic containers consist of one or more polymers together with certain additives. Those manufactured for pharmaceutical purposes must be free of substances that can be extracted in significant quantities by the product contained. Thus, the

hazards of toxicity or physical and chemical instability are avoided. The amount and nature of the additives are determined by the nature of the polymer, the process used to convert the plastic into the containers, and the service expected from the container. For plastic containers in general, additives may consist of antioxidants, antistatic agents, colors, impact modifiers, lubricants, plasticizers, and stabilizers. Mold release agents are not usually used unless they are required for a specific purpose.

Advantages of Plastic Containers

Plastic containers have a number of inherent practical advantages over other containers or dispenses. They are:

- Low in cost
- Light in weight
- Durable
- Pleasant to touch
- Flexible facilitating product dispensing
- Odorless and inert to most chemicals
- Unbreakable
- Leak proof
- Able to retain their shape throughout their use.
- They have a unique 'suck-back' feature, which prevents product doze.

If the quantity of the drug dispensed with one squeeze is more, relaxation of hard pressure permits the product to be sucked back into the tube. If this feature is undesirable for fear of contamination, plastic tubes designed to avoid suck back are available. Thus the suck back feature of plastic tubes can be an advantage or disadvantage. When the tube is partly empty, however, this feature is a nuisance, because the air must be expelled before the product can be dispensed.

Disadvantages

Plastics appear to have certain disadvantage like interaction, adsorption, absorption lightness and hence poor physical stability. All are permeable to some degree to moisture, oxygen, carbon dioxide etc and most exhibit electrostatic attraction, allow penetration of light rays unless pigmented, black etc. Other negative features include:

- **Stress cracking**, a phenomenon related to low density polythene and certain stress cracking agents such as wetting agents, detergents and some volatile oils.
- **Paneling or cavitation**, where by a container shows in ward distortion or partial collapse owing to absorption causing swelling of the plastic or dimpling following a steam autoclaving operation.
- **Crazing**, a surface reticulation which can occur particularly with polystyrene and chemical substances (e.g. isopropyl myristate which first cause crazing and ultimately reaches of total embitterment and disintegration).
- **Poor key of print** -certain plastics, such as the poly olefins need pretreating before ink will key. Additives that migrate to the surface of the plastic may also cause printing problem.
- **Poor impact resistance** – both polystyrene and PVC have poor resistance. This can be improved by the inclusion of impact modifiers such as rubber in case of polystyrene and methyl methacrylate butadiene styrene for PVC.

Majority of these effects can be either minimized or can be overcome by one or another means. For example, it was required to pack a nasal spray formulation in a plastic squeeze bottle which was available worldwide. This immediately called for a lowdensity polyethylene (LDPE) pack. The product however, contained a volatile preservative system, which both dissolved in LPPE and was lost from it by volatilization, thereby immediately suggesting that a conventional squeeze pack was unsuitable. The LDPE bottle was enclosed in a PVC blister impermeable to the volatile preservative and fitted with a peelable foil lid (also impermeable). As a result of this combination the loss of preservative was restricted to less than 5% of the total i.e. preservative soluble in the LDPE and preservative in the air space of the PVC blister reached a point where equilibrium was achieved between product, LDPE and the surrounding air space.

Materials

At present, a great number of plastic resins are available for the packaging of drug products. The more popular ones are:

Polyethylene

High-density polyethylene is the material most widely used for containers by the pharmaceutical industry and will probably continue to be for the next several years.

Polyethylene is a good barrier against moisture, but a relatively poor one against oxygen and other gases. Most solvents do not attack polyethylene, and it is unaffected by strong acids and alkalies. Polyethylene has certain disadvantages that it lack clarity and a relatively high rate of permeation of essential odors, flavors, and oxygen. Despite these problems, polyethylene in all its variations offers the best all-around protection to the greatest number of products at the lowest cost.

The density of polyethylene, which ranges from 0.91 to 0.96, directly determines the four basic physical characteristics of the blow-molded container: (1) stiffness, (2) moisture-vapor transmission, (3) stress cracking, and (4) clarity or translucency. As the density increases, the material becomes stiffer, has a higher distortion and melting temperature, becomes less permeable to gases and vapors, and becomes less resistant to stress cracking. The molecular structure of high-density material is essentially the, same as that of low-density material, the main difference being fewer side branches.

Since these polymers are generally susceptible to oxidative degradation during processing and subsequent exposure, the addition of some antioxidant is necessary. Usually levels of hundreds of parts per million are used. Antioxidants generally used are butylated hydroxy toluene or dilauryl thiodipropionate.

Antistatic additives are often used in bottle grade polyethylenes. Their purpose is to minimize airborne dust accumulation at the surface bottle during handling, filling, and storage. These antistatic additives are usually polyethylene glycols or long chain fatty amides and are often used at 0.1 to 0.2% concentration in high-density polyethylene.

Polypropylene

Polypropylene has recently became popular because it has many good features of polyethylene, with one major disadvantage either eliminated or minimized. Polypropylene does not stress-crack under any conditions. Except for hot aromatic or halogenated solvents, which soften it, this polymer has good resistance to almost all types of chemicals, including strong acids, alkalies, and most organic materials. Its high melting point makes it suitable for boilable packages and for sterilizable products. Lack of clarity is still a drawback, but improvement is possible with the construction of thinner walls.

Polypropylene is an excellent gas and vapor barrier. Its resistance to permeation is equivalent to or slightly better than that of high-density or linear polyethylene, and it is superior to low-density or branched polyethylene. One of the biggest disadvantages of polypropylene is its brittleness at low temperatures. In its purest form, it is quite fragile at 0°F and must be blended with polyethylene or other material to give it the impact resistance required for packaging.

Polyvinyl Chloride (PVC)

Clear rigid poly-vinyl chloride bottles overcome some of the deficiencies of polyethylene. PVC can be produced with crystal clarity, provide a fairly good oxygen barrier, and have greater stiffness. In its natural state, polyvinyl chloride is crystal clear and stiff, but has poor impact resistance. PVC can be softened with plasticizers. Various stabilizers, antioxidants, lubricants, or colorants may be incorporated. Polyvinyl chloride is seldom used in its purest form. PVC is an inexpensive, tough, clear material that is relatively easy to manufacture. PVC must not be overheated because it starts to degrade at 280°F, and the degradation products are extremely corrosive. Polyvinyl chloride yellows when exposed to heat or ultraviolet light, unless a stabilizer is included by the resin supplier. From the standpoint of clarity, the best stabilizers are the tin compounds, but the majority cannot be used for food or drug products. Dioctyl-tin mer-captoacetate and maleate compounds have been approved by the FDA, but these have a slight odor, which is noticeable in freshly blown bottles. Polyvinyl chloride is an excellent barrier for oil, both volatile and fixed alcohols, and petroleum solvents. It retains odor and flavors quite well and is a good barrier for oxygen. Rigid polyvinyl chloride is a fairly good barrier for moisture and gases in general, but plasticizers reduce these properties. Polyvinyl chloride is not affected by acids or alkalies except for some oxidizing acids. Its impact resistance is poor, especially at low temperatures.

Polystyrene

General-purpose polystyrene is a rigid, crystal clear plastic. Polystyrene has been used by dispensing pharmacists for years for containers for solid dosage forms because it is relatively low in cost. At present, polystyrene is not useful for liquid products. The plastic has a high water vapor transmission (in comparison to high-density polyethylene) as well as high oxygen permeability. Depending on the methods of manufacture and other factors, polystyrene containers are easily scratched and often crack when dropped. Polystyrene will build up static charge. Polystyrene has a low melting point (190°F) and therefore cannot be

used for hot items or other high-temperature applications. Polystyrene is resistant to acids, except strong oxidizing acids, and to alkalies. Polystyrene is attacked by many chemicals, which cause it to craze and crack, and so it is generally used for packaging dry products only. To improve impact strength and brittleness, general-purpose polystyrene may be combined with various concentrations of rubber and acrylic compounds. Certain desired properties like clarity and hardness diminish with impact polystyrene. The shock resistance or toughness of impact polystyrene may be varied by increasing the content of rubber in the material, and often these materials are further classified as intermediate-impact, high-impact, and super-impact polystyrene.

Nylon (Polyamide)

Nylon is made from a dibasic acid combined with a di-amine. Variety of nylons can be made with different dibasic acids and amines. The type of acid and amine that is used is characteristic and denotes the type of acid and amine used. e.g. nylon 6/10 has six carbon atoms in the diamine and ten in the acid. Nylon and similar polyamide materials can be fabricated into thin-wall containers. Nylon can be autoclaved and is extremely strong and quite difficult to destroy by mechanical means. Important to the widespread acceptance of nylon is its resistance to a wide range of organic and inorganic chemicals. As a barrier material, nylon is highly impermeable to oxygen. It is not a good barrier to water vapor, but when this characteristic is required, nylon film can be laminated to polyethylene or to various other materials. Its relative high-water transmission rate and the possibility of drug-plastic interaction have reduced the potential of nylon for long-term storage of drugs. Some of the nylon approved by FDA are Nylon 6, Nylon 6/6, Nylon 6/10, Nylon 11, and certain copolymers.

Polycarbonate

Polycarbonate can be made into a clear transparent container. Polycarbonate is expensive and offers some advantage that it can be sterilized repeatedly. The containers are rigid, as is glass, and thus has been considered a possible replacement for glass vials and syringes. It is FDA-approved, although its drug-plastic problems have not been investigated adequately. It is only moderately chemically resistant and only a fair moisture barrier. The plastic is known for its dimensional stability, high impact strength, resistance to strain, low water absorption, transparency, and resistance to heat and flame.

Polycarbonate is resistant to dilute acids, oxidizing or reducing agents, salts, oils (fixed and volatile), greases, and aliphatic hydrocarbons. It is attacked by alkalies, amines, ketones, esters, aromatic hydrocarbons, and some alcohols. Polycarbonate resins are expensive and consequently are used in specialty containers. Since the impact strength of polycarbonate is almost five times greater than other common packaging plastics, components can be designed with thinner walls to help reduce cost.

Acrylic Multipolymers (Nitrile Polymers)

These polymers represent the acrylonitrile or methacrylonitrile monomer. Their unique properties of high gas barrier, good chemical resistance, excellent strength properties, and safe disposability by incineration make them effective containers for products that are difficult to package in other plastic containers. Their oil and grease resistance and minimal taste transfer effects are particularly advantageous in food packaging. These type of polymers produce clear container and are less costly. The use of nitrile polymers for food and pharmaceutical packaging is regulated to standards set by the Food and Drug Administration. The present safety standard is less than 11 ppm residual acrylonitrile monomer, with allowable migration at less than 0.3 ppm for all food products.

Polyethylene terephthalate (PET)

Polyethylene terephthalate, generally called PET, is a condensation polymer typically formed by the reaction of terephthalic acid or dimethyl terephthalate with ethylene glycol in the presence of a catalyst. Although used as a packaging film since the late 1950s, its growth has recently escalated with its use in the fabrication of plastic bottles for the carbonated beverage industry. Its excellent impact strength and gas and aroma barrier make it attractive for use in cosmetics and mouth washes as well as in other products in which strength, toughness, and barrier are important considerations. Polyethylene terephthalate is used in food packaging and offers favourable environmental impact system.

Other Plastics

Co-extruded resins are being used to fabricate bottles and thermoformed blisters with barrier characteristics not previously attainable with single resins, resin blends, or copolymers. Co-extrusion technology permits the use of high-barrier resins, such as ethylene vinyl alcohol, which could not be used alone because of either cost or physical or dimensional instability. The resins used in the co-extrusion can be selected to provide optimum performance characteristics for the particular product needs. A co-extrusion such as

polypropylene/ethylene-vinyl-alcohol/polypropylene provides the moisture barrier of polypropylene coupled with the enhanced gas barrier of ethylene vinyl alcohol. The resins offers an alternative in packaging of products which were previously packaged only in glass containers.

High-barrier plastics that may compete with glass and metal containers may be available through a new processing technology developed by Du Pont Co. This technology involves dispersing nylon in a polyolefin resin so that the final polymer matrix contains a unique laminar arrangement of nylon platelets, which provide a series of overlapping barrier walls. Reportedly, this technique produces a plastic, which, when compared with the polyolefins, demonstrates a 140-fold increase as a barrier against certain hydrocarbons and an eightfold increase as a barrier for oxygen.

Product-Plastic interactions

Product-Plastic interactions have been divided into five separate categories:

(1) Permeation,

(2) Leaching,

(3) Sorption,

(4) Chemical reaction, and

(5) Alteration in the physical properties of plastics or products.

1) Permeation

The transmission of gases, vapors, or liquids through plastic packaging materials can have an adverse effect on the shelf-life of a drug. Permeation of water vapor and oxygen through the plastic wall into the drug can present a problem if the dosage form is sensitive to hydrolysis and oxidation. Temperature and humidity are important factors influencing the permeability of oxygen and water through plastic. An increase in temperature reflects an increase in the permeability of the gas. Great differences in permeability are possible, depending on the gas and the plastic used. Molecules do not permeate through crystalline zones; thus, an increase in crystallinity of the material should decrease permeability. Two polyethylene materials may therefore give different permeability values at various temperatures. Materials such as nylon, which are hydrophillic in nature, are poor barriers to water vapor, while such hydrophobic materials as polyethylene provide much better barriers. Studies have also revealed that formulations containing volatile ingredients might change when stored in plastic containers because one or more of the ingredients are passing through the walls of the containers. Often,

the aroma of cosmetic products becomes objectionable, owing to transmission of one of the ingredients, and the taste of medicinal products changes for the same reason. The physical system making up the product also may have an influence on the plastic container. For example, certain water-in-oil emulsions cannot be stored in a hydrophobic plastic bottle, since there is a tendency for the oil phase to migrate and diffuse into the plastic.

2) Leaching

Most plastic containers have one or more ingredients added in small quantities to stabilize or impart a specific property to the plastic and the prospect of leaching, or migration from the container to the drug product is present. Problems may arise with plastics when coloring agents in relatively small quantities are added to the formula. Particular dyes may migrate into a parenteral solution and cause a toxic effect. Release of a constituent from the plastic container to the drug product may lead to drug contamination and necessitate removal of the product from the market.

3) Sorption

This process involves the removal of drug content from the product by the packaging material. Sorption may lead to serious consequences active ingredients are in solution. Since drug substances of high potency are administered in small doses, losses due to sorption may significantly affect the therapeutic efficacy of the preparation. Sorption is seen mainly with preservatives. These agents exert their activity at low concentration, and their loss through sorption may be great enough to leave a product unprotected against microbial growth. Factors that influence characteristics of sorption from product are chemical structure, pH, solvent system, concentration of active ingredients, temperature, length of contact, and area of contact.

4) Chemical Reactivity

Certain ingredients that are used in plastic formulations may react chemically with one or more components of a drug product. At times, ingredients in the formulation may react with the plastic. Even micro-quantities of chemically incompatible substances can alter the appearance of the plastic or the drug product.

5) Modification

The changes in physical and chemical properties of the packaging material by the pharmaceutical product is called *modification.* Such phenomena as permeation, sorption, and

leaching play a role in altering the properties of the plastic and may also lead to its degradation. Deformation in polyethylene containers is often caused by permeation of gases and vapors from the environment or by loss of content through the container walls. Some solvent systems have been found to be responsible for considerable changes in the mechanical properties of plastics. Oils, for example, have a softening effect on polyethylene; fluorinated hydrocarbons attack polyethylene and polyvinyl chloride. In some cases, the content may extract the plasticizer, antioxidant, or stabilizer, thus changing the flexibility of the package. Polyvinyl chloride is an excellent barrier for petroleum solvents, but the plasticizer in polyvinyl chloride is extracted by solvents. This action usually leaves the plastic hard and stiff. Sometimes, this effect is not immediately perceptible because the solvent either softens the plastic or replaces the plasticizer; later, when the solvent evaporates, the full stiffening effect becomes apparent.

Constituents of plastic containers

The residues, additives and processing aids that may be used, and therefore possibly extracted from, plastic include:

- Monomer residues
- Catalysts
- Accelerators
- Solvents
- Extenders
- Fillers
- Slip additives
- Anti slip additives
- Antistatic agents
- Anti blocking agents
- Release agents

Most plastics include only a few of these constituents. Depending upon the additives used, other properties of the plastic can be changed, e.g. fillers such as chalk or talc are likely to increase moisture permeation.

Safety testing of plastics

Various testing procedures must be followed to ensure the safety of use of any plastic. Among this are biological, chemical, physical and pharmacological assessments. Greater

degree of safety testing is warned as the extend of contacts of the material with the plastic body increases. Thus intravenous solution container is studied in greater depth than in secondary packaging. Medical devices that are left intact in human body for prolonged periods of time (vascular grafts, parameters) are stupid most extensively. Their reactively and degree of toxicity must be determined. In all cases, it is imperative that the plastics and its processing procedure provide a non-reactive and non -toxic end product.

Biological testing procedures

To determine the suitability of plastic materials intended for use in fabricating containers or other accessories for both parenteral and ophthalmic preparations, many official USP biological procedures are designed. In case of parenteral and ophthalmic preparations the reaction of living animal tissues and normal animal to plastics is determined by injecting the extracts prepared from it. Depending on the use of plastic, other biological tests may be performed, such as pyrogenicity, blood compatibility, antigenicity, suitability for use in cardio vascular devices, embryological reaction and tissue toxicity testing.

Physiochemical testing procedure

Many physical and chemical test are applied on plastics, the particulars used depending on the intended application of the substances. The physiochemical procedures used by the USP are designed to determine the physical and chemical properties of plastics used as containers based on tests with extracts prepared by heating sample with water for injection at 70^0c for 24 hours. Portion of the extract are used to determined non-volatile residue, residue on ignition, heavy metals & buffering capacity or reaction, official limits for each which are specialized. The actual productivity package should be evaluated ensure product integrity throughout its shelf life. Potential incompatibilities between the primary plastic container and second packaging should be addressed to anticipate adulteration of the product. Prolonged exposure to UV light has been shown to enhance the migration of certain additives which in turn can accelerate the ageing characteristic of the plastic and decrease the shelf life of the product. Desirable features used for health care package are transparency, thermal stability, physical strength, formability, seal ability, biological carriers, radiation resistance and disposability. Quality assurance personal should periodically inspect the packaging lines and should check filled and labeled containers for compliance with written specification. These preservation sample should be retained for at least one year after the expiry date and should be stored in their original package and it should be consistent with product labeling.

COLLAPSIBLE TUBES

Metal

The collapsible metal tube is an attractive container that permits controlled amounts to be dispensed easily, with good re closure and adequate environmental protection to the product. The risk of contamination of the portion remaining in the tube is minimal, because the tube does not "suck back." It is light in weight and unbreakable, and it lends itself to high-speed automatic filling operations. The ductile metals used for collapsible tubes are tin *(15%),* aluminum (60%), and lead (25%). Tin is the more expensive than lead. Tin is the most ductile of these metals. Laminates of tin-coated lead provide better appearance and will be resistant to oxidation. They are also cheaper compared to tin alone. The tin that is used for this purpose is alloyed with about 0.5% copper for stiffening. When lead is used, about 3% antimony is added to increase hardness. Aluminum work hardens when it is formed into a tube, and must be annealed to give it the necessary pliability. Aluminum also hardens in use, sometimes causing tubes to develop leaks.

Tin

Tin containers are preferred for foods, pharmaceuticals, or any product for which purity is an important consideration. Tin is chemically inert of all collapsible tube metals. It offers a good appearance and compatibility with a wide range of products.

Aluminum

Aluminum tubes offer significant savings in product shipping costs because of their light weight. They provide good appearance.

Lead

Lead has the lowest cost of all tube metals and is widely used for nonfood products such as adhesives, inks, paints, and lubricants. Lead should never be used alone for anything taken internally because of the risk of lead poisoning. The inner surface of the lead tubes are coated and are used for products like fluoride toothpaste.

Linings

If the product is not compatible with bare metal, the interior can be flushed with wax-type formulations or with resin solutions, although the resins or lacquers are usually sprayed on. A tube with an epoxy lining costs about 25% more than the same tube uncoated. Wax linings are most often used with water-base products in tin tubes, and phenolics, epoxides, and vinyls

are used with aluminum tubes, giving better protection than wax, but at a higher cost. When acidic products are packed, phenolics are used and for alkaline products, epoxides are used.

Laminations

Permeation problems associated with plastic tubes, and corrosion and breakage problems experienced with metal tubes, have led to the emergence of another type of collapsible tube, the *laminated* tube. This tube, is constructed of a lamination containing several layers of plastic, paper, and foil, is fabricated from flat, printed stock. This lamination, which is specifically tailored to the product requirements, is welded into a continuous tube by heat sealing the edges of the lamination together in a machine called a "side seamer" and the tube is cut to desired length.

CLOSURES

The closure is normally the most vulnerable and critical component of a container in so far as stability and compatibility with the product are concerned. An effective closure must prevent the contents from escaping and allow no substance to enter the container. The adequacy of the seal depends on a number of things, such as the resiliency of the liner, the flatness of the sealing surface on the container, and most important, the tightness or torque with which it is applied. In evaluating an effective closure system, the major considerations are the type of container, the physical and chemical properties of the product, and the stability-compatibility requirements for a given period under certain conditions.

Functions of A Closure

- Provide a totally humetic seal.
- Provide an effective seal which is acceptable to the products.
- Provide an effective microbiological seal.

Charcteristics of The Closure

- It should be resistant and compatible with the product and the product /air space
- If closure is of re closable type, it should be readily operable and should be re-sealed effectively.
- It should be capable of high speed application where necessary for automatic production without loss of seal efficiency.
- It should be decorative and of a shape that blends in with the main containers.

Types of Closures

Closures are available in five basic designs

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

Many variations of these basic types exist, including vacuum, tamperproof, safety, child resistant, and liner less types, and dispenser applicators.

1. Threaded Screw Cap

The screw cap when applied overcome the sealing surface irregularities and provides physical and chemical protection to content being sealed. The screw cap is commonly made of metal or plastics. The metal is usually tinplate or aluminum, and in plastics, both thermoplastic and thermosetting materials are used. Metal caps are usually coated on the inside with an enamel or lacquer for resistance against corrosion. Almost all metal crowns and closures are made from electrolytic tinplate, a tin-coated steel on which the tin is applied by electrolytic deposition.

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. It is used to engage a lug on the cap sidewall and draw the cap down to the sealing surface of the container. Unlike the threaded closure, it requires only a quarter turn. The lug cap is used for both normal atmospheric-pressure and vacuum-pressure closing. The cap is widely used in the food industry because it offers a hermetic seal and handles well in sterilization equipment and on production lines.

2. Crown Caps

This style of cap is commonly used as a crimped closure for beverage bottles and has remained essentially unchanged for more than 50 years.

3. Roll-On Closures

The aluminum roll-on cap can be sealed securely, opened easily, and resealed effectively. It finds wide application in the packaging of food, beverages, chemicals, and pharmaceuticals.

The roll-on closure requires a material that is easy to form, such as aluminum or other light-gauge metal. Re sealable, non re sealable, and pilfer proof types of the roll-on closure are available for use on glass or plastic bottles and jars. The manufacturer purchases these closures as a straight-sided thread less shell and forms the threads on the packaging line as an integral part of the filling operation. The roll-on technique allows for dimensional variation in the glass containers; each roll-on closure precisely fits a specific container.

4. Pilfer proof Closures

The pilfer proof closure is similar to the standard roll-on closure except that it has a greater skirt length. This additional length extends below the threaded portion to form a bank, which is fastened to the basic cap by a series of narrow metal "bridges." When the pilfer proof closure is removed, the bridges break, and the bank remains in place on the neck of the container. The closure can be re sealed easily and the detached band indicates that the package has been opened. The torque is necessary to remove the cap.

5. Non-Reusable Roll-On Closures

In some packaging applications a reusable cap is not desired. Non-reusable caps require unthreaded glass finishes. The skirts of these closures are rolled under retaining rings on the glass container and maintain liner compression. Closures of this type have tear-off tabs that make them tamperproof and pilfer proof.

CLOSURE LINERS

A liner may be defined as any material that is inserted in a cap to effect a seal between the closure and the container. Liners are usually made of a resilient backing and a facing material. The backing material must be soft enough to take up any irregularities in the sealing surface and elastic enough to recover some of its original shape when removed and replaced. The backing material is usually glued into the cap with an adhesive, or the cap can be made with an undercut, so that the liner snaps into place and is free to rotate.

Factors in Selecting a Liner

Many factors have to be considered before an effective liner can be selected. The most important consideration is that the liner be chemically inert with its product, so that the latter is protected against any possible change in purity or potency. Gas and vapor transmission rates are usually relative and depend chiefly on the shelf life required for the product. If the

period between packing and consumer use is expected to be long, low transmission rates are necessary.

Homogeneous Liner

Homogeneous liners are one-piece liners available either as a disk or as a ring of rubber or plastic. Although they are more expensive and more complicated to apply, they are widely used for pharmaceuticals because their properties are uniform and they can withstand high temperature sterilization.

Heterogeneous or Composite Liners

Heterogeneous or composite liners are composed of layers of different materials chosen for specific requirements. In general, the composite liner consists of two parts: a facing and a backing. Usually, the facing is in contact with the product, and the backing provides the cushioning and sealing properties required.

Torque testing

Controlling cap tightness on a packaging line with a torque tester can prevent evaporation or leakage of the product, breakage of a plastic molded closure, and application of a cap too tight to be removed. The Owens-Illinois torque tester is an instrument commonly used for this purpose.

COMPOSITION OF CLOSURES

Closures are made of

- Rubber
- Plastics

Plastic closures

The two basic types of plastic generally used for closures are thermosetting and thermoplastic resins. They differ greatly in physical and chemical properties. And fundamentally different manufacturing methods are used for each type:

Thermosetting resins

Phenolic and urea thermosetting plastic resins are widely used in threaded closures. The thermosetting plastic first softens under heat and then curves and hardens to a final state. Shaping must occur in the first stage of softening, because after curving there is no further mobility, even upon reapplication of heat and pressure. During the molding process,

thermosets undergo a permanent chemical change, and unlike thermoplastic material, they cannot be reprocessed. Since parts that are improperly molded must therefore be discarded, thermosetting materials are usually fabricated by compression molding. The manufacturing process is relatively slow, but allows better control and quick response to change in temperature and material is slow.

Phenolics

Phenolic molding compounds are available in different grades and in dark colors, usually black or brown. Phenolic compounds are used when a hard sturdy piece is needed and when dark colors are well tolerated. Rigidity, heat, chemical resistance strengths are the outstanding properties of the phenolic compounds. Color limitation is the main drawback, although coatings are available at a premium price as a closure, the phenolic can withstand the torquing forces of the capping machines and maintains tight seal over a long period of time. The phenolic compounds are resistant to some dilute acids and alkalies. Organic acids and reducing acids usually do not have any effect. Strong alkaies decompose phenolic.

Urea

Urea is a hard translucent material. Urea is more expensive than the phenolic compounds, but the heat resistance and other properties of urea make it suitable for premium items. Elegant colours are obtained with urea because the translucency give brightness and color depth. Urea plastic is available in unlimited range of colours and is a hard, brittle material that is odorless and tasteless. Being a thermosetting plastic, urea can with stand high temperature without softening, but it chars at about 390^0F. Urea absorbs water under wet conditions, but such absorption has no serious effect on the plastic. Urea is not affectd by any organic solvents, but it is affected by alkaies and strong acids. Urea cannot be steam sterilized but can withstand elevated temperature. Parts may shrink as much as 0.003inch after molding.

Thermoplastics resins

Since their introduction, thermoplastic have become widely used in the manufacture of closures. Polystyrene, polyethylene and polypropylene are the materials used in 90% or more of all thermoplastic closures. Each material has specific performance advantage. The particular resins used depends on the physical and chemical properties desired for the particular products being packaged.

Rubber closures

Rubber is used in the pharmaceutical industry to make closures, cap liners and bulbs for dropper assemblies. The rubber stopper is used primarily for multiple dose vials and disposable syringes. The rubber polymers most commonly used are natural, neoprene and butyl rubber. Butyl rubber, nitrile rubber are some synthetic rubbers used for the manufacturing of closures.

In the manufacture of rubber closures the types of ingredients commonly found are:

- Rubber
- Vulcanizing agents
- Accelerator/ activator
- Extended filer
- Reinforced filler
- Softener / plasticizer
- Antioxidant
- Pigment
- Special components waxes.

Since the composition of rubber stopper is complex and the manufacturing process is complicated it is common to encounter problems with certain rubber formulas. For example, when the rubber stopper comes in contact with parenteral solution, it may absorb active ingredient, antibacterial preservative or other materials and one or more ingredients of the rubber may be extracted in to the liquid. These extractives could:

- Interface with chemical analysis of the active ingredient
- Affect the toxicity or pyrogenicity of the injectable product.
- Interact with the drug preservative to cause inactivation.
- Affect the chemical and physical sterility of the preparation so that particulate matter appears in the solution.

B.P requirmets for rubber closures

Rubber closures for containers used for aqueous parenteral preparations, powders and freeze dried products are made of materials obtained by vulcanization(cross-linking) of macromolecular organic substance (elastomers) with appropriate additives.

Rubber closures may be classified in to two types

- **Type I closures** are those which meet the stringent requirements and are the one mostly preferred.
- **Type II closures** are those which having mechanical properties suitable for special uses (for e.g. Multiple piercing), cannot meet requirements as severe as those for the great category because of their chemical composition.

The Closures Chosen for Use With A Particular Preparation Are Such That

- The components of the preparation in contact with the closure are not absorbed onto the surface of the closure.
- The closure does not yield to the preparation substance in qualities sufficient to affect its stability or to present a risk of toxicity.
- The closures are compatible with the preparation for which they are used throughout its period of validity.

The manufacturer of the preparation must obtain from the supplier an assurance that the composition of the closure does not vary and that it is identical to that of the closure used during compatibility testing. When the supplier informs the manufacturer of the preparation of changes in the composition, compatibility testing must be repeated, totally or partly, depending on the nature of the changes. The closures are washed and may be sterilized before use.

Tests to control quality of rubber caps

This include tests for

1) Quality

The closures should not be techy after:

- Washing with detergent and rinsing several times.
- Autoclaving at 121^0C for half an hour in distilled water.
- Drying at 65^0c in vacuum for a day.

2) Finish

Closures must be substantially free from dust, fibers, loose particles of rubber, smears of grease and pigment and quite free from internal foreign matter.

3) Penetrability

The closure is sealed into a vial and the force required to make a hypodermic needle penetrate is measured using the piercing machine. The vial is moved on to the needle at a specified speed. The force must not exceed a stated value.

4) Fragmentation

Test is carried out by using piecing machine with the vial. The vials are half filled with particle free water. Each closure is penetrated with a hypodermic needle (0.08mm external diameter) within a limited area and the last time the needle is washed to transfer fragments from bore to vial. Then the contents are filtered through paper (pore size 0.5mm) of a color that contrasts with the rubber and the fragments are counted by eye. The test is carried out on 20 closures using a fresh needle for each if the previous one has become blunt. These must not be more than average of 3 fragments per closure.

5) Self sealability

Two tests are applied:

- In the first, closed vials, half filled with water are inverted and air, equal to the volume inside, is injected. Then the needle of water from the hole or more than a droplet on the surface.
- In the second, methylene blue solution is used instead of water and 25 needle punctures are made evenly within a circle of 5mm diameter to which a prescribed vacuum is applied (or reduced pressure of 27Kpa for 10 minutes, kept for 30 minutes in atmospheric pressure) for half an hour. There must be no signs of leakage in the water or on the closure.

6) Water extractive Test

Extraction with boiling water is made under reflux for four hours and evaporated to dryness. Weight of the residue must be not more than 2mg for type I and not more than 4mg for type II rubber.

7) Acid or Alkali Treatment

Specified number of closures are autoclaved with a given volume of freshly boiled and cooled distilled water of P^H 6.8 – 7.2. The acid or alkali needed for the neutralization of this extract should be within the limit, i.e. not more than 0.3ml of 0.01M sodium hydroxide or 0.8ml of 0.01 hydrochloric acid.

8) Compatibility with contents

- Sterile products are packed aseptically in sterile containers and are stored at 4^0, $25^{0,}$ 38^0 and 50^0C with prescribed humidity.
- A control is done using a satisfactory rubber closure or ampoule.

After One Year Examine For

1. Foreign insoluble matter, using standard conditions of illumination.
2. Loss of potency and preservatives and increase in toxicity (compared with the controls).
3. Signs of deterioration of the closures such as sponginess and discoloration. The latter should be checked after drying overnight because absorption of water and certain solutes often produce a bleached appearance. It must also pass the tests of the standard for penetrability, self sealability and fragmentation.

9) Permeability to Water Vapor

The increase in weight of vials containing dry fused calcium chloride is found after storage under the high humidity conditions and compared with the result for containers sealed with closures known to be satisfactory. Weightings are made fortnightly for 3 months.

10) Absorbance

Rubber cap with 200ml water is autoclaved. Filtered the autoclaved solution through 0.45mm pore sized paper. Measure absorbance at 20-360 nm. Absorbances should not exceed 0.2 for type I & 4 for type II.

11) Test to Determine Liberation of Toxic Substances Form Rubber

The test involves the preparation of a blood plate, which is then flooded with a heavy inoculum of Streptococcus pyogenes. Previously sterilized rubber samples are placed on the surface and incubated at 37^0C for 18 to 24 hours. The red blood cells are haemolysed if organisms are growing and therefore there will be rings of un haemolysed blood around the samples if inhibitory substance are liberated.

Other Requirements

- After ageing at 70^0c for 168h, the closures must self seal, when placed with the large needles (2.4mm in diameter) used in transfusion sets.
- They must be of a specified hardness.

- After ageing and fitting to a transfusion bottle, they must withstand specify exposures to cold and steam under pressure without impairment of function. E g, they should not become sticky or lose resilience.

12) Limit Test

When treated with ammonium and heavy metals the limit must be nmt 2ppm.

13) Titration

Rubber in presence of 200 ml water for injection is autoclaved at 121^0C for half an hour to 20 ml of 0.002M potassium permanganate. Boil and cool (3mins). Add 1g of potassium iodide & titrate with 0.01 M $Na_2S_2O_3$ using 0.25 ml of starch solution as indicator. Perform a blank titration. Difference of titration values should be nmt 3ml for type I and 7ml for type II closure.

Shipping Cartons

Shipping cartons for liquids in cans and bottles, bulk solids in jars, pouches, and folding boxes, and items with or without individual packaging are usually made of corrugated craft paper. The most common styles are the Regular Slotted Carton (RSC), the end opening RSC, and the center special full overlap slotted container. End joints may be stapled, stitched, glued or taped. Specifications include dimensions of length, width, and depth, in that order. When boxes are set up and closed by automatic equipment, dimensional tolerances become critical. Cartons are shipped knocked down to the user from plants located in all industrial centers. Because order lead time is 4 to 6 weeks, inventories of empty boxes require considerable space. Often, the size of items packaged in corrugated cartons either does not permit interlocking of layer of cartons, or leaves considerable void space between them. Since calculating by hand the best size of carton for maximum palletizing density requires considerable effort, computer software is available. Examples are CAPE by CAPE systems, Plano, Texas and TOPS Engineering Corporation.

Stages in The Development of A Package Product Combination

The stages broadly associated with packaging developments are as follows:

1) Pre Formulation

Pre formulation studies are essential for all packaging components. This provide information relating to the limitations of the packaging material.

2) Product Formulationa

All formulations are required to be documented and stored. It is therefore necessary to make certain that all packaging materials are defined and that all packaging parameters (torque, heat, seal etc.) are identified, controlled and documented (all part of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) during formulation studies).

3) Consideration of Container Materials

It is important to have a basic knowledge of all packaging materials, their properties, characteristics etc. and the process by which they are fabricated/ decorated as a packaging container or component, as well as how these and any subsequent process may affect their properties, e g: sterilization by ethylene oxide can lead to ethylene oxide and ethylene glycol residues. Gamma radiation of low density poly-ethylene marginally reduces the flexibility owing to molecular cross linkage and can give rise to formic acid and formaldehyde residues.

4) Pack Feasibility Tests

This is the stage where a product (preferably the formulation selected for / ultimate scale) is tested in a range of possible package, usually over a range of conditions from say 20^0C to 45^0C, together with alteration in temperature –humidity range. In addition to the storage tests indicated above the immersion of pieces of package or package components if plastic, in the product or a stimulant i.e. an extractive-type-test may also be employed. Extractive tests are usually mandatory for plastics used for injectables and ophthalmic products. Feasibility tests usually extend over a period of 1-12 months. Only after a period of normally 3-6months any decision about the package is taken.

5) Formal Stability Test

Formal stability test is conducted only after a suitable package –product combination is selected. By conducting the formal stability test, the shelf life of a product can be determined. Test conditions has been specified by the International Conference on Harmonization and adopted by the major regulatory bodies in Europe, The USA and Japan. Normally three large-scale batches of product in each package is selected. For long term stability test purpose the temperature is maintained at 25^0C with a relative humidity of 60% and in case of accelerated stability test, the temperature is maintained at 40^0c with a relative humidity of 75%. The samples are kept over a period of 5 years and examinations are conducted at the intervals of 0 (optimal), 3,6,9,12,18,24,30,36,48 and 60 months. The data generated are send to the regulatory authorities as part of the marketing authorization application.

6) Ongoing Stability

This consist of repeated stability on random batches from production in order confirm that the shelf life does not change during the manufacture of each batch.

7) Complaints

This is the final means of monitoring the success of the product and pack. It is somewhat similar to the monitoring and recording of adverse reactions in that it is a safeguard to both the company producing the drug and the person receiving it. In all the above tests analytical and packaging technological support is essential to check both the product and the package.

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. More detailed information usually should be provided for a liquid-based dosage form than for a powder or a solid, since a liquid-based dosage form is more likely to interact with the packaging components.

Table 4: 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

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 Vapor 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.

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 nonvolatile 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. Coupling MS to LC and GC methods provides a definitive and effective tool for identifying unknown impurities and degradation products.

Other changes such as pH shifts, precipitates, and discoloration, which may cause degradation of pharmaceutical product must be evaluated. Changes in the physical characteristics of the container, such as brittleness must be evaluated using thermal analysis

and hardness testing. 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.

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. Determining the safety of a packaging component is not a simple process, and a standardized approach has not been established. However, an extraction study should be one of the first considerations. Isolation is accomplished through sample preparation, followed by incubation in solvents at well-defined and well-controlled times and temperatures. Sample preparation is an area in which an experienced chemist's knowledge of chemical procedures is indispensable.

Prior to performing any of the chemical tests, it is important to have precise information on the synthesis of the polymer itself. This includes descriptions of the monomers used in the polymerization, the solvents used in the synthesis, and the special additives that have been added during material production. For containers used to package drugs ranked with a high degree of concern, such as inhalation aerosols and injectables, this type of information is imperative. Knowledge of degradation products that may be released into the drug product is also important.

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). These tests are particularly useful in defining materials as rich or poor in extractable chemicals. The tests categorize material extracts in general terms, such as nonvolatile residue (total extractables), residue on ignition, buffering capacity, heavy-metals content, and turbidity.

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.

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.

Table 5: Typical Suitability Considerations for Common Classes of Drug Products.

Route Of Administration/ Dosage Form	Suitability			
	Protection	Compatibility	Safety	Performance/ Drug Delivery
Inhalation Aerosols and Solutions, Nasal Sprays	L, S, M, W, G	Case 1 c	Case 1 s	Case 1 d
Inhalation Powders	L, W, M	Case 3c	Case 5s	Case 1d
injections, Indictable Suspensions	L, S, M, G	Case 1 c	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 1 c	Case 2s	Case 2d
Topical Delivery Systems	L, S	Case 1 c	Case 3s	Case I d
Topical Solutions and Suspensions, and Topical and Lingual Aerosols	Case 3s	L, S, M	Case 1c	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
Oral Powders	L, W	Case 2c	Case 3s	Case 3d
Oral Tablets and Oral (Hard and soft Gelatin) Capsule	L, W	Case 3c	Case 4s	Case 3d

Explanation of the codes in the table

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: Indicates the USP Biological Reactivity Test data, extraction /toxicological evaluation, limits on extractable, and batch-to-batch monitoring of extractable.

Case 2s: Indicates the USP Biological Reactivity Test data and possibly extraction/toxicological evaluation.

Case 3s: Indicates 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: Indicates an appropriate reference to the indirect food additive regulations is sufficient.

Case 5s: Indicates 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 Id: Frequently a consideration.

Case 2d: May be a consideration.

Case 3d: Rarely a consideration.

Guideline on General Principle of Process Validation

Installation qualification- Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerance.

Process performance qualification - Establishing confidence that the process is effective and reproducible.

Product performance qualification - Establishing confidence through appropriate testing that the finished product produced by a specified process meets all requirements for functionality and safety.

Prospective validation - Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

Retrospective validation - Validation of a process for a product already in distribution based upon accumulated production, testing and control data.

Validation - Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Validation protocol - A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

Worst case - A set of conditions encompassing upper and lower processing limits and circumstances, it including those within standard operating procedures, which pose the greatest chance of process or product j failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

While the above definitions are specifically for processing, they apply to packaging as well. In specifying packaging equipment, it is necessary to include all of the above considerations.

In general, primary packaging adopted requirements are used. These include many of the following, but this is just a sampling requirement in all companies, but they are usually specified

- 316L Stainless Steel, Electroplated
- Elastomers that are seamless silicon or Teflon
- Equipment designed to minimize the particulate contribution to the environment
- Drive systems for conveyors, star wheels, turntables and robotic mechanisms located below the tabletop in enclosed spaces
- Lubricated components located in enclosed spaces
- Enclosed spaces should be properly designed and sealed to prevent cleaning agents and lubricants from seeping in or out of the space.
- Exposed surfaces shall be designed for complete wipe down.

- Materials must be non-corrosive, non-toxic and non-abrading.

Exposed exterior surfaces of the system shall be compatible with the following disinfectants formaldehyde, quaternary ammonium compounds, per acetic acid, and phenolic compounds.

In secondary packaging some of the requirements specified are as follows

- Cleanability
- Eliminate hidden or constrained areas of the machine where labels, cartons, inserts, tablets, etc.
- Cannot be found. Total cleanout of each packaging machine is an FDA requirement.
- Many manufacturing companies prefer stainless steel construction.
- Materials for filling non-sterile products should be non-corrosive, non-toxic and non-abrading.
- Materials for filling non-sterile products may be required to be wipedown.
- Bar code scanning for labels, cartons, product inserts and other printed material
- OCV (Optical Character Verification) or OCR (Optical Character Recognition) is usually specified to read any code data that is printed on labels and cartons.
- Vision inspection equipment for product inspection
- Vision inspection equipment for package integrity

Purchasing Pharmaceutical Packaging Equipment

Once the specifications are developed, the vendor selection and purchasing process begins. Vendors selected should be familiar with Good Manufacturing Practice (GMP'). Documentation packages require probably more extensive than would be required in other industries. Many companies now are including some of the validation programs to assist the customer. Some companies sell validation packages as extras to go with the machines and some are including them in the base price. These traditionally include the Installation Qualification (IQ) and the Operational Qualification (OQ).

Acceptance of Equipment

To insure that equipment will meet GMP, most manufacturers require and perform extensive Factory Acceptance Tests (FAT's) at the vendors. Placebos sometimes are needed for filling tests because of the toxicity or cost of the product. These should be prepared to meet the product characteristics as closely as possible to insure success. Some manufacturers will do

some of the IQ and OQ testing during these FAT's. Others will wait until the equipment is commissioned and installed.

Installation and Start up of Equipment

Each manufacturer has different methods for installing and starting up equipment. Usually the equipment is installed, commissioned and validated. This can be done with internal personnel or with external personnel. In some cases, a building contractor or engineering firm will perform the installation and commissioning. There are also firms that specialize in commissioning and validation. For new installations, it may be preferable to use some outside assistance. In many cases, the vendor will assist in the installation as well.

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 the for 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.

FDA REGULATIONS

Food and Drug Administration evaluates a drug and the agency must be firmly convinced that the package for a specific drug will preserve the drug's efficacy as well its purity, identity, strength and quality for its entire shelf life. Under the provisions of the Food and Drug Administration Act, however, no specifications or standards for containers or container closures are provided. Under the Act, it is the responsibility of the manufacturer to prove the safety of a packaging material and to get approval before using it for any pharmaceutical

product. The Food and Drug Administration does not approve containers as such, but only the materials used in the container are approved. A list of substances considered "Generally Recognised As Safe" (GRAS) has been published by the FDA. In the opinion of the qualified experts they are safe under specified conditions, assuming they are of good commercial quality. A material that is not included under GRAS or prior sanction, and is intended to be used with food, must be tested by the manufacturer, and the data must be submitted to the FDA.

The specific FDA regulation states that "containers, closures and other component parts of drug packages, to be suitable for their intended use, must not be reactive, additive or absorptive to an extent that the identity, strength, quality or purity of the drug will be affected." The packaging material must be approved for such use, along with the drug, before going to the market. The drug manufacturer must include data on the container and package components in contact with the pharmaceutical product in its New Drug Application (NDA). If the FDA can determine that the drug is safe and effective, and that the package is suitable, it approves the drug and package. Once approved, however, the package may not be altered in any manner without prior FDA approval. In the case of plastics, most resin manufacturers maintain Master Files on their resins with the FDA. Upon request from the resin manufacturer, the FDA uses this file as a reference to support a New Drug Application that which a drug manufacturer files.

Robotics

The introduction of robotics has given a new dimension to packaging in that it is now possible to do repetitive tasks with speed and accuracy at notably lower cost than if done by people. The manufacturer of robots is well established providing a quality product with continuity of service, supply and software support. Economic analysis needs to be done before making the decision as to whether to automate doing robots, fixed automation, or the labor of people aided by work aids.

There are two principle classes of robots. One type involves a fixed position for a central control and manipulator unit. This type of device is particularly useful where a repetitive motion is required, such as taking a package component from one position and then rapidly and accurately placing it in another position. The robot functions in an X-Y-Z axis basis. This permits the device is perform relatively crude tasks such as picking up a component, orienting it, and then moving it to the desired place and precisely positioning it in the X., Y or

Z planes. The term package components can mean any part of the package itself or the product which is to be packaged.

A second type, generally regarded as being more versatile than the fixed point robot is the gantry robot. This device also offers capability of the X, Y and Z directions. Programming is usually more simple for the gantry than for the fixed-position robot. The gantry robot can also use a manipulator at its pickup and discharge points. This often is as simple as a clamp or a device that has its own X-Y-Z degrees of freedom.

A robot often can be economically justified when the task of doing a certain packaging operation is analyzed in detail. When the work rids are considered and their cost determined the additional cost for providing robot capability is often of a small magnitude, which justifies, it is to replace human labor. There are many examples where a single operator controls an entire production and packaging operation where robotics do all of the manual tasks. The robots are under the direction of their software. The operator is often a person who has at least an associate in science degree from a country college. Programming languages used for robots is becoming more standardized. This allows robotic equipment to be reused many times after the original operation has been abandoned.

The Child Resistant Packaging

The definition of Child Safe Packaging is "packaging that is difficult for a child to open within a reasonable period but that presents no difficulty for an adult to use properly and flexible packages with hidden tear starts or peel back and push blister packs did and still do present problems for elderly or handicapped people to use properly. The Child-Safe Packaging Group (CSPG) was formed eleven years ago and its objective is to promote the specification and success of child resistant packaging systems for all products whose ingestion or other contact could prove seriously distressing to a child.

The Child-safe Packaging Group has been a catalyst for the introduction two new standards: one British and the Pan-European which will help to create better flexible packs. A new standard for rigid packs has been published, this again will make them more acceptable to adults and help to banish forever the old quip about adults not being able to access their medicines when packed in child resistant packs because child resistant packaging remains the only packaging for any product which has to be tested for openability by adults. It has already

and will continue to make for a more consumer acceptable pack and the system of testing for adult openability could well be applied to packaging generally.

The report of the inquest into the circumstances surrounding the death of three year old Yaqoob Lookman, published in most national newspapers on Thursday August 3rd, has been described by members of the Child-Safe Packaging Group as predictable, avoidable and the result of pure negligence. Briefly, the child swallowed 44 ferrous sulfate tablets, which he extracted from two blister packages. The Child-Safe Packaging Group had declared this type of packaging to be dangerous since its own research was published in 1995. Blister packages are tested for child resistance in the United States, Canada and Germany. Pharmaceuticals and other hazardous products are packaged in either rigid or flexible containers. Rigid packaging systems, bottle and child resistant closure, are subject to testing for child resistance and have been so since 1975.

The Child-Safe Packaging Group consists of the greater part of the supply industry for re closable packaging systems for pharmaceutical or other hazardous products. The Child-Safe Packaging Group commissioned research in 1995 that conclusively proved that blister packages in common use in the United Kingdom and other European countries were not child resistant. The results of this research were announced in the press then and have subsequently been referred to in papers published by the group and debates in the packaging and pharmaceutical industries.

Economic Growth and Marketing Strategy

Pharmaceutical and medical device industries are under the same pressures as other manufacturing industries to do more with less and to deliver higher quality and value to customers. One way for companies to meet both demands is to automate their operations. Companies would be wise to employ machine vision systems in addition to relying on robotics and automation to mechanize their manufacturing, packaging, and labeling operations. The Automated Imaging Association conducts a study each year to identify industries of potential growth for machine vision systems. While final results of the most recent study are not in, preliminary results suggest that the market for machine vision in the pharmaceutical industry increased 15-20% in 1997 to approximately $35 million following a 25% increase from 1995 to 1996.

Many companies with drugs under development are already moving to attain high throughput screening by automating. Many feel that their survival depends upon the speed with which they automate drug development. US demand for Pharmaceutical Packaging products will increase by 4.3 per cent per year to US $ 5.2 billion in 2006. Blister packaging will remain the leading product group, generating average annual growth of six per cent. Expanding unit dose, compliance, clinical trial, high barrier and high visibility applications will impact favorably on demand. Pouches and strip packages will also see above average growth based on adaptability to low-cost unit dose formats.

Pre-fillable inhalers will account for the strongest value gains among all pharmaceutical packaging products as design innovations boost applications in the delivery of asthma and allergy medication. Pre-fillable syringes will generate better than average demand growth based on emergency response time and infection prevention advantages over vials and ampoules.

Reflecting cost, regulatory compliance and ease-of-use benefits, dual child-resistant and dispensing closures will fare the best among pharmaceutical packaging accessories in the marketplace. Blister packages will account for over 20 per cent of this amount, gaining growth momentum from widening uses in clinical trials and over-the-counter medication. The combination of compliance and high visibility features will boost the popularity of these containers throughout the drug producing industry. Paperboard boxes and cartons will continue to account for the largest sales gains among secondary pharmaceutical containers. Increasing applications in the high value-added packaging of over-the-counter drugs, herbal supplements, nutraceuticals and alternative medicines will spur growth. Pharmaceutical packaging accessories will generate weaker gains in sales value than pharmaceutical containers. Demand for medication closures will lose growth momentum due to the increasing penetration of blister packages and other closureless containers. Among all medication closures, combined senior-friendly, child-resistant types will fare the best in the marketplace based on strengthened government and industry standards involving the ease-of use and protective features of pharmaceutical Packaging. In packaging, companies continue to shift toward using more plastic. Plastic containers are replacing glass containers, plastic and laminated flexible packaging is replacing paper, and plastic closures are replacing metal ones. Machine vision systems can both control the respective manufacturing processes and sort out products that would be objectionable to consumers.

Machine vision options are now being offered by a number of suppliers of automated and intelligent labelers to ensure label quality as well as placement accuracy and consistency, and to verify date/lot code imprints via OCR or 2-D symbology reading. The increased use of pressure-sensitive labels has also driven the adoption of automated and intelligent labelers with product/label verification systems. The dietary supplement industry, which has been less than sensitive to labeling concerns, is coming under increased FDA scrutiny and developing a heightened awareness to consumer concerns regarding label and package issues.

Because of vision systems, packaging lines are becoming more flexible without sacrificing throughput. When simple sensors are used to verify line functions, changeover times inevitably increase and physical position changes are often required. A machine vision-based sensor system can be set up once for each product or package handled by a line, and changeover can be initiated easily through a single graphical user interface. This changeover could even include physical changes in camera optics with computer-controlled zoom lenses or servomotors.

Perhaps the most important trend affecting machine vision is the recognition that data can yield insights into machine performance and line productivity on a function by function basis. Machine vision is fundamentally one of the most intelligent data collectors. Interpreting and acting on the trends detected by machine vision systems can make filling and packaging lines far more productive while delivering optimized quality. Engineers should consider employing such systems to ensure product quality while expediting their operations.

The production of pharmaceutical packaging products will account for raw material consumption valued at US$875 million in 2006, up 3.3 per cent annually, from 2001. Plastic resins will continue to account for the largest value based on breadth of applications, cost advantages and favourable intrinsic and processing properties. Paper and paperboard will also generate significant demand, serving as the leading materials for drug labels and secondary containers. The third leading pharmaceutical packaging raw material, aluminium foil, is projected to provide the strongest growth opportunities, which will evolve from expanding applications in blister and strip packs and pouches. Glass will sustain significant demand in small-volume parenteral vials, ampoules and prefillable syringes, but will continue to lose end uses to plastics in oral medication bottles and prescription vials. Based on applications in speciality IV and parenteral closures, rubber and elastomers will provide the best growth opportunities among other pharmaceutical packaging raw materials.

Pharmaceutical Packaging-Void Fill and Cushioning Options

A carton may be filled with a number of different products that require protection during transit. Inevitably there will be a mix of large and small, heavy and light and some products that require a higher degree of protection than others. Selecting the right type of void fill is essential to minimize damage, maintain a positive customer relationship and successfully manage the budget. It could justifiably be argued that cushioning and void fill products are not at the glamorous end of the packaging industry. They are often the last packaging item to be considered, often when the rest of the packaging budget has been used. However, these types of products are equally important in developing an overall packaging strategy for the company. Importantly, the type of void fill selected must be functional, cost-effective and offer an improved environmental performance over traditional materials.

Void fill packaging is the last thing that goes in the carton and is the first thing that the recipient of the package sees when they open it. Consequently, there are numerous considerations to take into account when selecting the type of cushioning material to use. Production will have a different perspective to marketers. Fulfillment companies and contract packagers will require different attributes to a single station packing line. These days the packager has more choice than ever. The type of cushioning or void fill will usually be based on the following criteria: functional performance, ease of use, speed of packing, cost, environmental performance and customer acceptance.

Early Void Fill Products

Early packagers would have had to rely on products such as wood wool, paper and bubble wrap as void fill products. However, these products experienced technical flaws as void fill materials and have been superseded. The major problem with some of the early products was that they were very slow and inflexible to work with. They often required manual stuffing of the carton, which was very labor intensive and costly. Products such as wood wool were also dusty and did not create the type of image that brand managers were looking for.

Polystyrene Loose Fill Chips

The next big breakthrough came in the form of flowable polystyrene loose fill chips. This product was a revelation to packagers that wanted cleaner, faster, more flexible packaging. Polystyrene loose fill has been an important void fill product for over two decades. The chips flow around the product being packed, occupying all of the voids in the carton to give a high degree of protection. Numerous brands have been sold worldwide, all with different colors

and shapes to aid brand recognition. One thing that they all have in common is that they are an effective void fill and have helped companies dramatically reduce the cost of packing in the warehouse. In high throughput warehouses, the loose fill can be pneumatically conveyed from trucks outside the warehouse to large overhead storage silos located above the packing line. Lower volume users may use small portable silos that contain one or two cubic meters of loose fill. However, since the early 1990s polystyrene sales have come under new pressure.

Focus on Blow/Fill/Seal Technology

Strong emphasis on the science of Blow/Fill/Seal technology as it relates to the optimization of machine design to enhance process capabilities relating to sterility assurance**.** These efforts are recognized by the worldwide regulatory community by applying the results of scientific research to the design of the design of the next generation Blow/Fill/Seal machines are firmly setting the standards to the highest level of sterility assurance for aseptic technology. The Asep-Tech® Model 628 Blow/Fill/Seal machine from Weiler Engineering, Inc. features a two-piece stepped base design for easy maintenance and convenient product discharge. All existing Model 624 tooling (molds, fill systems, parison heads) can be used on the Model 628 machine, making it an attractive upgrade for current users. The versatile Model 628 has the flexibility to produce sterile, liquid filled, tamper-evident containers ranging in size from 0.5ml up to 250ml, in full scale production quantities. Several other machine models are offered to fulfill higher output and/or larger container size requirements.

Blow/ Fill/ Seal Process

The ASEP-TECH System automatically delivers a finished package in five steps

1. Thermoplastic resin is extruded into a tubular shape called a parison.
2. When the parison reaches the proper length, the mold is closed and the parison is cut. The bottom of the parison is pinched closed and the top is held in place. The mold is then conveyed to a position under the blowing and filling nozzle.
3. The blow-fill nozzle is lowered into the parison until it forms a seal with the neck of the mold. The container is formed by blowing sterile filtered compressed air into the parison and expanding it against the walls of the integrally cooled mold cavity. Next, the sterile air is vented from the container and the sterile product is metered into the container through the fill nozzle, which then retracts.
4. Separate sealing molds close to form the top and hermetically seal the container.

5. The mold opens, and the formed, filled and sealed container is conveyed out of the machine.

Future Prospects in Pharmaceutical Packaging

A patented electronically controlled fill system, an automatic sterilization system (SIP) with integral data acquisition, and a filter integrity test system are provided as standard equipment for each machine configuration. Each machine is also equipped with a HEPA air shower to assure a Class C environment under dynamic conditions in the nozzle shroud area. Accessories are available for the ASEP-TECH Blow/Fill/Seal System, including a transport cart to assist with tooling conversion, a stainless steel buffer tank to help assure accurate control of stringent fill requirements, and custom barrier isolation systems for container designs requiring inclusion of injection molded components as part of the aseptic package.

Applications

The ability to provide sterile liquid products that meet corporate, scientific, regulatory and end-user requirements can be a demanding task in today's environment. In ASEP-TECH® Blow/Fill/Seal technology several machine models are available to choose from, designed to manufacture containers ranging in size from 0.2ml to 1000ml at production rates of up to 15,000 units per hour, depending on container configuration.

- Small Volume Parenterals (SVP's)
- Large Volume Parenterals (LVP's)
- Ophthalmic's
- Respiratory therapy

CONTRACT PACKAGING

Contract packaging is a great way for manufacturers of packaged goods to relieve pressure on their packaging capacity. Users of contract packaging can start-up companies that cannot or do not want to invest in packaging lines right away, or established product manufacturers. Among the latter, it's common to use contract packagers for new products, as a way to avoid establishing a new line until the product's success is assured. This option is especially attractive when the new product requires packaging equipment that the manufacturer doesn't yet have.

In general contract packaging involves accepting product in bulk and packaging it, or accepting it in a certain package form and switching or combining it into another form.

Contract manufacturers formulate the product before packaging it. Flexibility is an important aspect of a contract packager's operation. Contract packagers are often called upon to switch package sizes many times during the day; their equipment should be designed to minimize changeover time, preferably with servo-operated equipment, or at least with well-established changeover procedures.

An ideal contract packaging operation should be transparent, meaning that the customer-the product manufacturer-should be able to inspect the line at will. The contract packager should also be able to assist the customer in replicating the packaging process if and when the customer decides to take it in-house. The customer should have full access to production and quality data from the packaging line. Contract packaging operations range from very small ones to affiliates of large machinery or materials suppliers. The former are especially flexible, especially for small applications like regional, seasonal or test markets. The latter often can offer focused expertise connected to their particular line of machinery or materials. Some storage and logistics providers provide contract packaging services, also. These sometimes have a direct tie-in with the kind of storage they provide, such as frozen food packaging with frozen storage. Logistics providers often can offer excellent tie-ins with a customer's existing software packages, such as an enterprise resource planning system.

Cloud Packaging Solutions

Cloud Packaging Solutions prides itself on providing complete solutions to its customers. Cloud Packaging Equipment, Cloud Engineering Services and Cloud Packaging Services provide a range of solutions from manufacturing packaging equipment to project management to contract packaging. Cloud's business groups work together, allowing the company to be a single-source solutions provider from concept to consumer. In supplying high-speed integrated packaging systems, and providing contract packaging services, Cloud focuses on developing technologies that give the company a competitive advantage. Cloud delivers highly efficient, reliable and cost-effective solutions for both primary and secondary packaging. Solutions from Cloud allow for high speeds, accurate feeding, consistent seals, high yields, reduced labor and good efficiencies.

Standard and Speciality Packaging Solutions For The Pharmacuetical Industry

Attractive, wallet based specialty packaging solution are developed by Rondo along with the sister company Dividella. These solutions are used for child resistant package (CRP) and also ensure safe shipment.

Advantages of these are

- The contents of the package are clearly visible
- The products are easily accessible.
- Product leaflet lie on top of the products.
- All package component can be replaced easily in the package.
- Additional information can be printed on the other side of the cover.

Traceable Solutions for Medical Packaging

The demand for safety and integrity in the area of medical packaging has taken on new and significant implications in the past two or three years. Child safety, correct dosage, patient traceability, tampering and diversion of pharmaceuticals are always an area of concern, medical packaging. Now, major additional concerns of drug counterfeiting and concerns around terrorism bring a new sense of urgency to medical packaging manufacturers and hospitals, clinics, assisted living facilities, doctors' offices and, the individual consumer.

Proponents of unit dose packaging like the Healthcare Compliance Packaging Council (HCPC), the National Quality Forum (NQF) and others recognize that packaging plays a major role in safeguarding healthcare. And of course, various government agencies, most notably the Federal Food and Drug Administration (FDA) have very stringent packaging regulations and enforcement. The pharmaceutical industry in particular will be one of the drivers of new packaging identification technology like RFID, expected to be a viable means of medical packaging traceability. And though RFID is an evolving technology it will be some number of years before it is an individual solution at the unit dose level, as it is currently being used at the pallet and case levels due to costs and still to be solved technology issues. Bar coding and RFID technologies co-exist for several years.

There are considerable steps yet to be taken to ensure packaging traceability. At this point, for example, only some manufacturers have affixed unit-of-use barcodes to hospital injectable drugs and / or intra venous solutions. Tracing pharmaceuticals from their origin at a chemical plant to the patient bedside is the ideal, and may be eventually attainable when RFID is completely embedded throughout the medical packaging world. While safety and compliance are critical issues, the drive to keep costs under control and manufacture and package product in the most efficient manner is an additional dimension that manufacturers, as well as pharmaceutical distributors, pharmacies and others must constantly address.

Convenience at the point of usage also drives certain packaging requirements, particularly in a hospital, clinical or assisted living environment.

Advantages

Traceable packaging can address many safety as well as business concerns. In an ideal packaging environment, with full traceability from process to patient (or consumer) these concerns can be addressed:

- **Fraudulent Products** - Drug counterfeiting is a problem that must be addressed. Internet drug sales contribute to this issue. The World Health Organization estimates that fraudulent drugs generate $32 billion dollars in annual earnings for drug counterfeiters.
- **Expired Products** - Medicines sold as fresh after their expiration dates is a problem easily addressed if traceable packaging is implemented.
- **Diverted Products** - Again, a system of traceable packaging can keep track of pharmaceutical product locations in the complex distribution system.

If we look at a few concerns within clinical, hospital or assisted living settings there are several issues addressed through traceability. For example

• **The wrong medicine to the wrong patient** - In an assisted living facility it is estimated that approximately 44 percent of the patients require seven or more medications per day. With the level of medications dispensed in hospitals and clinics on a daily basis, making sure the correct medicine goes to the correct patient every time is a critical issue.

• **Incorrect Dose** - The issues are obvious here and traceability, where the dosage is one of the identified properties, is a solution.

• **Drug Incompatibility** - Being aware of other medications taken by patients, or conditions like food requirements are concerns that can be addressed to some extent by traceable packaging.

These are just a few of the areas where packaging traceability can add value from a business perspective

- **Supply Chain Management** - The ability to track inventories, ensure proper supplies, and improve inventory management are all benefits, particularly as RFID packaging becomes available at the individual bag level.
- **Inventory Control** - A key part of supply chain management, tracking inventory throughout the cycle, will result in definite cost saving realizations.

- **Drug Recalls** - The ability to better manage drug recalls is a benefit not only to the manufacturer but to the government as well. Traceability will ease this complex process.

While we have pointed out a few of the concerns and the accompanying benefits that traceable packaging can provide to the medical packaging industry and the consumer, there are many steps yet to be taken.

Rondo - fluted trays

For all low fragile product needs, whether they are made from glass, metal, plastic or wood, anything that needs special packaging considerations and still should be clearly visible, with the help of rondo fluted trays. The contents can be easily removed and put back after every use.

Together with consumer friendly carton boxes *"Rondo -fluted trays"* offers many advantages

- Products are clearly visible
- Products are easily removable
- Additional information can be printed on the inside cover of the package

NeoTop Concept

The paperboard packaging solutions developed are all erected, filled automatically on the packaging line from die cut flat blanks. Later they are provided with a tamper evident seal. NeoTop 904 is used for ampoules, vials, pre-filled syringes or small tubes. NeoTop 304 is used for:

- Ampoules 1 vials I to 100 ml
- Cartridges / syringes - bottles up to 52 mm diameter
- Inhalers, nasal sprays, pens and other applications

Reverse Side Printing

Marketing experts around the world have come to realize that the inside of the package can be successfully utilized to bring more information to their customers. Depending on the branch, there are different goals that can be achieved. For example: the pharmaceutical industry can put a product description or a pictogram, the cosmetic industry has a place to enhance the product attractiveness.

The **advantages** are higher quality product, increased time savings and a noticeably lower cost.

Coding In Pharmaceutical Packaging

Coding and marketing have many functions in pharmaceutical packaging. They provide expiry dates for perisable products, lot and date codes to aid in tracing and recalls, bar codes, sales messages and other important information .A barcode (also bar code) is a machine readable representation of information in a visual format on a surface. Originally barcodes stored data in the widths and spacings of printed parallel lines, but today they also come in patterns of dots, concentric circles, and hidden in images. Barcodes can be read by optical scanners called barcode readers or scanned from an image by special software. Barcodes are widely used to implement Auto ID Data Capture (AIDC) systems that improve the speed and accuracy of computer data entry. While traditionally barcode encoding schemes represented only numbers, newer symbologies add new characters such as the uppercase alphabets. The drive to encode more information in combination with the space requirements of simple barcodes led to the development of matrix codes which do not consist of bars but rather a grid of square cells. Stacked barcodes are a compromise between true 2D barcodes and linear codes, and are formed by taking a traditional linear symbology and placing it in an envelope that allows multiple rows.

Technology of barcodes

A linear barcode is a binary code (1s and 0s). The lines and spaces are of varying thickness and printed in different combinations. To be scanned, there must be accurate printing and adequate contrast between the bars and spaces. Scanners employ various technologies to "read" codes. The two most common forms are lasers and cameras. Scanners maybe fixed position, like most supermarket checkout scanners, or hand-held devices, often used for the taking of inventories. There should be (but typically is not) a distinction drawn between the code, which is a structure for the conveyance of data, and the symbol, the machine-readable representation of the code: The code is text, which can be translated into a multiplicity of languages - English; French, Japanese, symbol.

The universal product code

The Universal Product Code or UPC is unique because it was developed by the user community. Most technological innovations are first invented and then a need is found for the

invention. The UPC is a response to a business need first identified by the US grocery industry in the early 1970s.

Symbologies

The mapping between messages and barcodes is called a symbology. The specification of a symbology includes the encoding of the single digits/characters of the message as well as the start and stop markers into bars and space, the size of the quiet zone required to be before and after the barcode as well as the computation of a checksum.

Linear Symbologies Can be Classified Mainly by Two Properties

- **Continuous vs. discrete**: Characters in continuous symbologies abut, with one character ending with a space and the next beginning with a bar, or vice versa. Characters in discrete symbologies begin and end with bars; the intercharacter space is ignored, as long as it is not wide enough to look like the code ends.
- **Two-width vs. many-width:** Bars and spaces in two-width symbologies are wide or narrow, how wide a wide bar exactly has no significance as long as the symbology requirements for wide bars are adhered to (usually two to three times more wide than a narrow bar). Bars and spaces in many-width symbologies are all multiples of a basic width called the module; most such codes use four widths of 1, 2, 3 and 4 modules.

Scanners (barcode readers)

The earliest, and still the cheapest, barcode scanners are built from a fixed light and a single photosensor that is manually "scrubbed" across the barcode. A later design, the "laser scanner," uses a polygonal mirror or galvanometer-mounted mirror to scan a laser across the barcode -initially only in a straight line, but eventually in complicated patterns so the reader could read barcodes at any angle. In the 1990s some bade reader manufacturers began working with digital cameras to capture barcodes, both linear and 2D. That technology has since been perfected and now often surpasses laser scanners in performance and reliability. More recently, off-the-shelf digital cameras now have enough resolution to capture both 1D and 2D barcodes. Increasingly companies are looking to incorporate barcode scanning software into camera phones.

Historically, pharmaceutical packaging requirements focused exclusively on preserving the quality of the enclosed medication and increasing the products shelf lives. These requirements are now being extended to cover such criteria as the prevention of product

tampering and counterfeiting, the assurance of product dispensing accuracy, child protection and the promotion of patient compliance with product dosage schedules. Pharmaceutical noncompliance is a tremendous problem in the US, resulting in an estimated $100 billion expense every year while being blamed for the deaths of over 1,25,000 Americans annually (342 people every day). Ten percent of all hospital admissions are the result of pharmaceutical noncompliance and 23% of all nursing home admissions are as a result of people's inability to take their medications as prescribed. In February 2004, FDA published the final version of 21 CFR Parts 201, 606 and 610 to reduce the number of medication errors in hospitals and healthcare settings. The rule specifies that the packaging of all human drugs be labelled with a linear bar code containing the National Drug Code (NDC) number that serves as a universal product identifier. This 10 digit code identifies the labeler/vendor, product, trade package size, the specific strength, the dosage and the formula for a specific firm.

According to the Healthcare Compliance Packaging Council (HCPC), the National Quality Forum (NQF) and FDA, the implementation of unit dose blister and strip packaging places a further restraint on the intentional or accidental misuse of pharmaceuticals. Furthermore, the European Union (EU) specifies that all prescription drugs dispensed directly to patients be in a unit dose packaging. FDA describes unit dose packaging as the only packaging format that can accommodate bar codes on packaging labels for each dosage of medication dispensed to patients. Coding and marking technologies for the primary packaging of pharmaceuticals must constantly evolve to meet the emerging industry trends and associated regulations. Bar coding methods have been traditionally chosen according to three main criteria.

- The kind of data required to appear on the bar code (numeric symbols, alpha-numeric or special characters).
- The amount of available space on which to print and the specific location of the bar code.
- Where the bar code needs to be placed near an edge, there is a considerable risk of misreads (when a scanner cannot read the bar code).

There is a wide variety of printers available for coding and marking pharmaceutical primary packaging including thermal transfer, inkjet, dot-matrix, laser, flexographic and color change. It is not easy for companies to choose the appropriate technology that would suit their specific needs. The right choice depends upon the company's top priorities regarding legibility, cost, speed, ease-of-use, cleanliness and security.

Thermal transfer and inkjet printers

Thermal transfer and inkjet printers are more appropriate for production line bar code printing. Specifically, thermal transfer printers produce high quality, legible and clear bar codes, as well as other types of codes. Because ink is not involved, there is never any quality degradation during the process. Moreover, such printers are virtually maintenance free while they can also be connected to a software network for record keeping purposes, which helps with validation. The main drawback of this technology is that although it can be set up quickly, it lacks printing speed.

Inkjet Printers

Inkjet printers are the fastest and least expensive units available on the market. Unfortunately, there are considerable limitations to what they can print. In addition, they require frequent maintenance and can be quite messy. Another major downfall is that the print fades after successive use. Water-based inkjet fluids tend to streak and blur, while non water, soluble inkjet fluids produce a shine that reflects to the scanner and affects how the bar code is read.

Dot -Matrix printers

Dot -Matrix printers produce low-quality codes with low contrast, although this depends on the ribbon used.

Laser printers

Laser printers are off-line devices requiring a separate label applicator. They are subjected to toner flaking, meaning that they are unreliable for long-term bar code printing.

Laser marking by ablation

Laser marking by ablation is more recent method uses a high powered beam to ablate the bar code onto the label by burning away a black ink patch to form the white spaces by exposing the underlying substrate material. However, this method results in high emission levels and can also create problems for bar code resolution levels.

Flexo Graphic printers

Flexo Graphic printers produce high-quality images, thereby being most suitable for printing small characters but they can be costly to use and maintain because a plate change is required for every coding change.

Color change technology

Color change technology is a non contact, high resolution, low emission technique that generates high definition data, bar codes and graphics to an infinite array of materials. Combining chemistry, substrate conversion and laser energy, this process uses very low power laser light for the high speed, on-demand printing of variable information on primary packaging. The subsequent laser imaging process provides a means of marking without ablation and it does not require any ink or ribbons. Additionally, the technology is virtually maintenance free, non-toxic and environmentally friendly. Color change technology is equally suitable for any type of primary packaging substrate including flexible packaging, paper, board and plastics. The technology's versatility makes it ideal for a wide range of applications relating to coding, marking, and tracking and tracing. Because of the stability of the image produced, this solution provides extreme protection for brand integrity.

New products and technologies in specialty inks for packaging

- **Aroma:** Adding scent packaging is a new way to differentiate and enhance a product.
- **Fluorescents**: These bright colors create shelf impact.
- **Glitter:** Improvements include better controlled spread across the roller on a printing press.
- **Lamination**: New RotoPure® HS lamination ink, which provides adhesion and high-lamination bonds, can be printed at high speeds {up to 2,000 feet per minute).
- **Laser-engravable primer:** For coding/marking, packagers now have the option of any color combination, not just white on dark surfaces. This can also be used to add Braille to a package because the laser mark creates a bubble in the ink.
- **Matte:** Low gloss inks offer a new option of creating matte designs which have gained in popularity recently.
- **Metallic:** New innovations include high-luster metallic inks printed on a holographic image to create eye-catching designs. Other improvements include maintaining their shiny appearance on shrink labels, instead of turning dull gray, which they had a tendency to do before.
- **Metameric:** These inks are only visible through a specific color spectrum.
- **Phosphorescent:** Recent improvements include a long lasting effect and a smaller particle size, which means the ink can now be printed on a flexographic press, as well as gravure and silkscreen.

- **Photochromic:** These inks change color in ultraviolet light.
- **Security:** Used far overt and covert brand security. Covert ink need special instruments to view them. One example (of many) is use of taggants that glow under black light.
- **Tactile:** By adding texture, these inks not only appeal to the eye. They also invite consumers to touch and handle a package, helping them connect emotionally with the product.
- **Thermochromic:** These inks which change color depending on the temperature, can be reversible or irreversible.
- **Track and-Trace:** Conductive inks can be used as the antennae for Radio Frequency Identification (RFID) chips.

In summary, scientists working in the pharmaceutical packaging industry should base their choice of printing technology on three main criteria First, the regulations governing pharmaceutical practice, second, their company's specific coding and marking needs, and third, the benefits and downfalls each particular method involves.

Radio Frequency Identification in Packaging (Rfid)

Radio frequency identification (RFID) is one of the biggest trends to hit packaging in years. Radio Frequency Identification (RFID) is a powerful technology that promises to streamline supply chains and transform the retail ecosystem. It promises a slew of benefits to manufacturers and retailers alike, including unprecedented control over the supply chain and enhanced product security. The FDA has stepped up its efforts to improve the safety and security of the nation's drug supply by encouraging use of a state-of-the-art technology that tags product packaging electronically. The technology, called radiofrequency identification, or RFID, allows manufacturers and distributors to more precisely track drug products through the supply chain. RFID makes it easier to ensure that drugs are authentic, and it also creates an electronic pedigree-a record of the chain of custody from the point of manufacture to the point of dispensing. Electronic pedigrees will improve patient safety and protect the public health by allowing wholesalers and retailers to rapidly identify, quarantine, and report suspected counterfeit drugs and conduct efficient, targeted recalls. An RFID tag may be a little sticker that can be attached to an object. The tag contains an antenna that enables it to receive and respond to a radiofrequency query from an RFID device called a transceiver. Most RFID tags in use today do not have their own power supply. The radiofrequency query induces a tiny electrical current in the antenna, permitting the tag to send a brief response,

usually just an ID number. Such RFID tags are quite small. The smallest tags are now commercially available measure 0.4 □ 0.4mm and are thinner than a sheet of paper. They start at about $0.40(40 cents) a tag.

By outfitting drug packages with RFID tags, drug companies, distributors, and pharmacists can trace the path the drugs take from the time they are produced to the moment they are dispensed RFID involves the use of electronic tags with computer chips that can store data. The tags, affixed to pallets, shipping cases or individual packages, transmit their data to reading systems, enabling shipments to be recorded and tracked throughout the supply chain. Some forms of tags are battery-powered, but "passive" or "backscatter" tags are more common; these derive their power from the reader's signal.

AUTO LABEBOOTH 4556

Auto Labe's Model 110SR RFID label applicator uses the latest radio frequency identification (RFID) reader technology for encoding EPC data directly to an RFID label prior to application. This is an apply-only solution for customers who do not require online printing of RFID labels. The 110SR drive system uses the latest technology to provide consistent and accurate label placement. In November 2004, the FDA published a compliance policy guide for industry on implementing RFID studies and pilot programs. Acting FDA Commissioner Dr. Lester M. Crawford says the agency's actions were designed with one main goal: "to increase the safety of medications consumers receive by creating the capacity to track a drug from the manufacturer all the way to the pharmacy".

Purdue Pharma (Stamford, CT), the maker of OxyContin and Palladone, among other prescription and non-prescription drugs, last November was one of the first to launch a pilot program to integrate RFID tags at the item-level for two of its largest customers: Wal-Mart and drug wholesaler H.D. Smith. The pilot, which places RFID tags on the labels for 100-tablet bottles of OxyContin, is just the start of Purdue Pharma's major RFID initiative and multi-layered security approach. The drug manufacturer is also pursuing other overt and covert measures to safeguard its products. The goal: To transform the way Purdue Pharma packages and ships medications in order to deter counterfeiting and diversion, and to track the authenticity and safety of its products throughout the entire pharmaceutical supply chain.

The U.S. Food and Drug Administration (FDA) is also concerned about the counterfeiting trend; it released a report last year to promote and assist companies looking to adopt RFID

throughout the drug-distribution system. While the FDA maintained drug counterfeiting isn't yet a widespread problem, it acknowledged that the number of FDA investigations surrounding counterfeit cases is on the rise. The FDA now looks into more than 20 cases a year since the year 2000, up from around five annually in the 1990s. The report, which do not specify any deadlines for RFID's use. The RFID technology showed the most promise as a means for tracking and tracing a drug's "pedigree" – a record of the drug as it moves through the supply chain showing it was manufactured and distributed under safe and secure conditions. Typically, if a pedigree exists at all in today's world, it's achieved with a paper trail. Using RFID tags, the FDA report contends, companies could achieve mass serialization, meaning they could assign a unique number (the electronic product code) to each pallet, case and package of drugs and then use that number to record information about all the transactions involving the product. As a result, a drug purchaser could immediately determine critical factors such as a drug's authenticity, where it was intended for sale and whether it was previously dispensed. The FDA sketched out a timeline for RFID implementations, predicting that a variety of companies would conduct feasibility studies in 2004 and 2005, with more widespread adoption and deployment of RFID throughout the pharmaceutical supply chain by 2007.

The shift towards this technology has to a large extent being dictated by large buyers like WAL–Mart, Retail gaint WAL–Mart began the use of RFID tagging last year to replays barcodes. The technologies is the more advanced version of bar coding and is likely to result in greater cost savings in the long run by improving the efficiency of the supply chain. According to Sathish Reddy, MD and CEO, DR. Reddys Laboratories the company is in the process of introducing RFID for its exports of finished dosage formulation to the USA in order to comply with customers requirements. According to Ranbaxy, The RFID chip fixed under the lable, contains all relevant information like manufactures name, batch No etc. Ranbaxy and Dr. Reddys Laboratories will soon have products with RFID tags in the US.

The scope of the compliance guide is based on information the FDA obtained concerning RFID feasibility studies examining the use of this technology for various business purposes, including inventory control and tracking and tracing of drugs. To encourage these studies, the guide announces the FDA's intention to exercise enforcement discretion if certain studies trigger regulatory requirements.

- A manufacturer, repackager, relabeler, distributor, retailer, or others acting at their direction will attach RFID tags (chips and antennae) to only immediate containers, secondary packaging, shipping containers, and/or pallets of drugs that are being placed into commerce. There is no limit to the number of tags or readers that may be used in the study.
- RFID will be used only for inventory control, tracking and tracing of products, verification of shipment and receipt of such products, or finished product authentication.
- RFID will not be used to fulfill existing FDA regulatory requirements (e.g., fulfillment of labeling or Current Good Manufacturing Practice requirements, provision of chemistry, manufacture, and control information, storage of information in fulfillment of a regulatory requirement, or performance of label and product reconciliation).
- Information, storage of information in fulfillment of a regulatory requirement, or performance of label and product reconciliation).
- RFID will not be used in lieu of current labeling control systems to ensure correct labeling processes.
- The study will use "passive," "semi-active," or "active" tags.
- Information will be written to the tag at the time the tag is manufactured (e.g., "read only" tags), after the tag is manufactured but before it is affixed to a drug's container (e.g., "read-write tags"), or after the tag is affixed to a drug's container. The tags will contain a serial number (e.g., an electronic product code) that uniquely identifies the object to which the tag is attached, and may also contain other information such as storage and handling conditions, information from the FDA approved label and labeling, lot number, and product expiration date.
- The tags will not contain or transmit information for the healthcare practitioner.
- The tags will not contain or transmit information for the consumer.
- The tags will not contain or transmit advertisements or information about product indications or off-label product uses.
- A seal containing a logo, an inventory control message unrelated to the product (e.g., a message informing the custodian that the package contains an RFID tag), and/or a unique serial number may be placed over the RFID tag or elsewhere on a drug's immediate container, secondary packaging, and/or shipping container.
- The addition of the RFID tag and seal will not block, obscure, or alter any of the product's existing and approved label and labeling information.

- The RFID tag will not substitute for, replace, or interfere with a linear bar code. Participants will "read" the tags as needed to identify the product and/or conduct the study.
- The tag readers will work by emitting electromagnetic energy at radio frequencies of 13.56 megahertz, 902-928 megahertz, or 2.4 gigahertz, and at powers in compliance with regulatory requirements of the Federal Communications Commission (i.e., 1-4 watts effective iso tropically radiated power).

CONCLUSION

Packaging should provide protection, identification, information, convenience and compliance for a product during storage, carriage, display and until such time the product is consumed. A thorough background about the product, the market, the distribution system and other facilities available have to be considered while selecting a packaging material. Pharmaceutical packaging should look into concerned issues like child safety, correct dosage, patient traceability, tampering and diversion of pharmaceutical products. Now, major additional concerns of drug counterfeiting and concerns around terrorism bring a new sense of urgency to medical packaging manufacturers and hospitals, clinics, assisted living facilities, doctors' offices and, the individual consumer. Considerable steps have to be taken to ensure packaging traceability. Some manufacturers have affixed the use of barcodes to pharmaceutical products. Tracing pharmaceuticals right from their origin at a chemical plant to the patient beside may be attainable when Radio Frequency Identification (RFID) is embedded throughout the pharmaceutical packaging and makes it easier to ensure that the product is authentic and thereby improves the efficiency of drug supply chain.

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