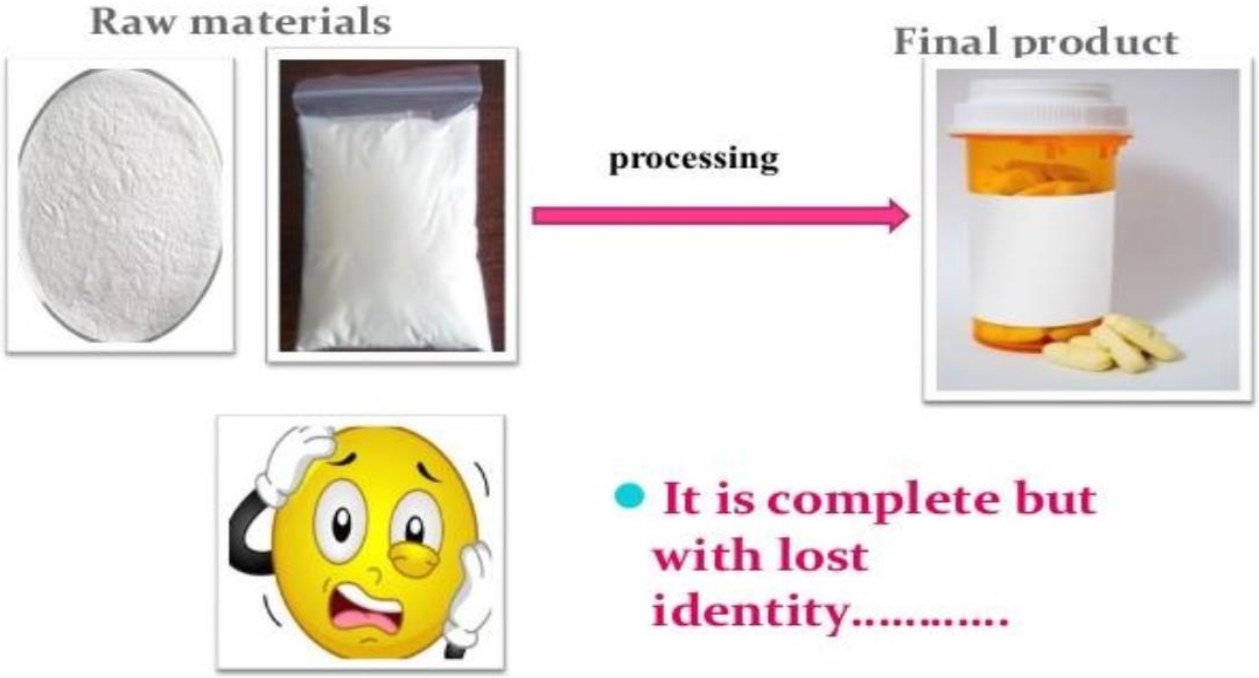
Pharmaceutical labelling

A **prescription drug** is a pharmaceutical drug that legally requires a medical prescription to be dispensed. In contrast, **over-the-counter drugs** can be obtained without a prescription. The reason for this difference in substance control is the potential scope of misuse, from drug abuse to practicing medicine without a license and without sufficient education. Different jurisdictions have different definitions of what constitutes a prescription drug.

"**Rx**" is often used as a short form for prescription drug in North America. Prescription drugs are often dispensed together with a monograph (in Europe, a Patient Information Leaflet or PIL) that gives detailed information about the drug.



Why is labeling of drug is so important?

- ❖ Inherent risks
- ❖ Risks due to interactions with other drugs
- ❖ Risks due to disease states
- ❖ Risk of over and under dosage

Rx Drugs

- Physician information
  - Package insert
  - Information sheets for physicians
- Depends on expertise of physician

- Rarely, patient package insert
    - When patients have significant control over choice of drugs
    - Birth control pills

OTC

- On the box
- Insert in the box
- Must allow safe use by consumer
- Labeling issues often determine whether a drug is OTC or Rx

Labels can make the drug

- Apple Cider Vinegar alone is not a drug
    - Apple Cider Vinegar with a label that says it will cure cancer is a drug, subject to FDA regulation
    - Also Subject to FTC Regulation
- Does a book saying it treats cancer make it a drug?
- Is the author guilty of misrepresentation?

FDA Standards

- A drug is misbranded if:
    - [Its] "labeling is false or misleading in any particular" or
    - The labeling does not bear "adequate directions for use."
- Drugs are misbranded if the manufacturer does not use the FDA approved label information
- Misbranded products cannot be sold

Federal trade commission standards

- Misleading or deceptive
- FTC looks at all advertising and promotional materials
- Penalties
    - Civil fines
    - Criminal prosecution
- Usually secondary to the FDA for drugs
- Governs medical products that are not under the FDCA

Tort Law Standards

- Must provide full prescribing information
- Must provide all side-effects and contraindications
- Must anticipate misuse and warn against it
- Must quickly add any new information about the drug

FDA Standard for an Rx Drug Label

Labeling must include the established name, proprietary name (if any), adequate directions for use, and adequate warnings. The agency considers the approved product labeling, sometimes called the full prescribing information, to be adequate directions for use and adequate warning.

What the Label Cannot Have?

- Unapproved Uses
  - Only Uses From Approved NDAs
  - Hence "Off-Label" Uses
- Disputes with the FDA
- No Over-Warning
  - CYA in Tort Cases
  - Interferes with Rational Prescribing

Manufacturers have the most information

- Clinical Trials Under The IND
  - Proprietary Information
  - Controlled By The Manufacturer
  - Should Be Reported To The FDA
- Post-Market Information
  - Manufacturer Gets Primary Reports
  - Should Pass Information To The FDA

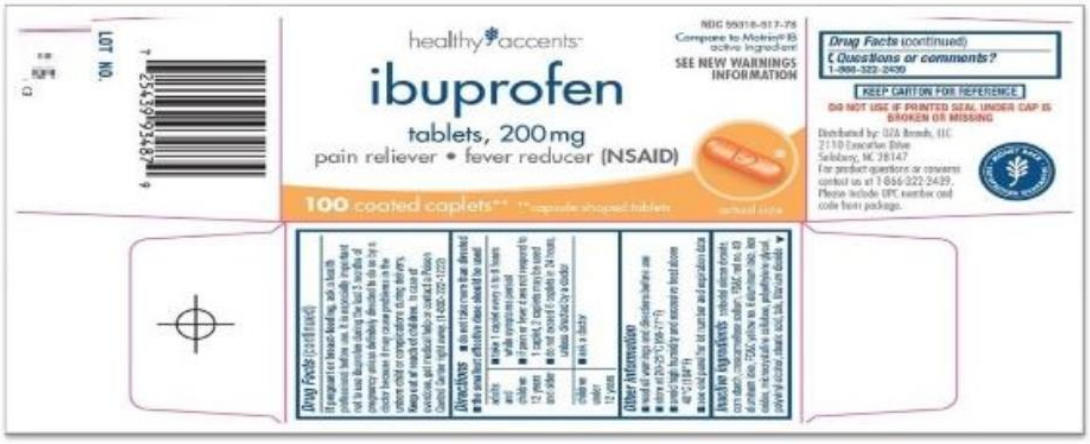
Label – I

"Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference)".

Label – II

"For use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the FD&C Act."

Need of a label



Label means a display of written, printed or graphic matter upon immediate container or the wrapper of a drug package.

Types of label

1. Manufacturer label
2. Dispensing label

Manufacturer label

A label, which contains drug information for the use of medical practitioners, pharmacists, or nurse supplied by the manufacturer, packer or distributor of the drug (FDA).

Legal requirements of a Manufacturer label

- The name of preparation
- Strength and dosage form
- Quantity
- Instruction for the use
- Precautions and warnings

- Registration number
- Batch number
- Manufacturing and expiry date
- Price
- The name and address of pharmaceutical industry

The name of preparation

Generic name:

According to drug labeling and packaging rules 1986: "International non-proprietary name means the name of a drug as recommended by WHO or may be notified by the federal government in the official gazette"

Brand name:

- Brand name is used to market the drug
- Property of drug company

Strength

It is amount of active drug / unit dose

Eg:

Amoxicillin, 250mg capsules and Amoxicillin, 500mg capsules

Specification

- U.S.P
- B.P

USP specifications

The **United States Pharmacopeia (USP)** is a pharmacopeia

(compendium of drug information) for the United States published annually by the **United States Pharmacopoeial Convention** (usually also called the USP), a nonprofit organization that owns the trademark and copyright.

The USP is published in a combined volume with the National Formulary (a formulary) as the **USP-NF**.[2] If a drug ingredient or drug product has an applicable USP quality standard (in the form of a USP-NF monograph), it must conform in order to use the designation "USP" or "NF." Drugs subject to USP standards include both human drugs (prescription, over-the-counter, or otherwise), as well as animal drugs.

USP-NF standards also have a role in U.S. federal law; a drug or drug ingredient with a name recognized in USP-NF is deemed adulterated if it does not satisfy compendial standards for strength, quality or purity. USP also sets standards for dietary supplements, and food ingredients (as part of the Food Chemicals Codex). USP has no role in enforcing its standards; enforcement is the responsibility of FDA and other government authorities in the U.S. and elsewhere.

BP Specifications

The **British Pharmacopoeia** (**BP**) is the national pharmacopoeia of the United Kingdom. It is an annual published collection of quality standards for UK medicinal substances. It is used by individuals and organizations involved in pharmaceutical research, development, manufacture and testing.

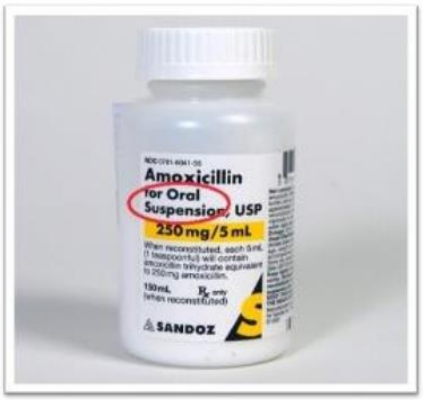
Pharmacopoeial standards are publicly available and legally enforceable standards of quality for medicinal products and their constituents. The British Pharmacopoeia is an important statutory component in the control of medicines which complements and assists the licensing and inspection processes of the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom. Along with the British National Formulary (BNF), it defines the UK's pharmaceutical standards.

Pharmacopoeial standards are compliance requirements; that is, they provide the means for an independent judgment as to the overall quality of an article and apply throughout the shelf-life of a product. Inclusion of a substance in a pharmacopoeia does not indicate that it is either safe or effective for the treatment of any disease.

Dosage form

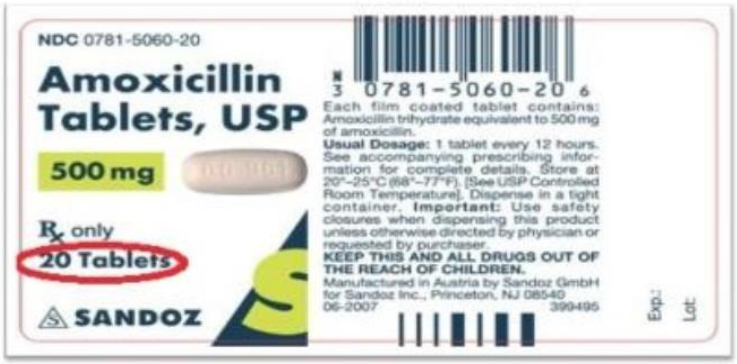
Dosage form of the medicine should be mentioned on the label.

Eg: different dosage forms of amoxicillin



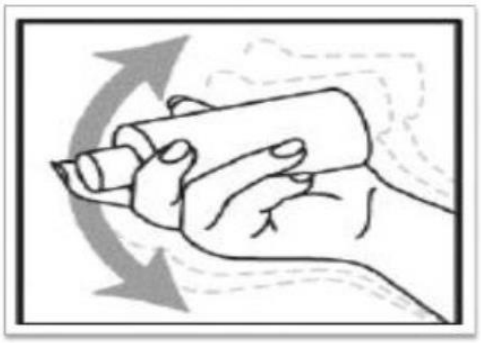
Quantity

Quantity / volume present per a packaging unit



The container holds 20 tablets and each tablet has a dosage strength of 500mg / tablet.

Instructions



Shake well before use:

Necessary to all disperse systems.

- Emulsions
- Suspensions Eg: Liniments, Lotions, Tinctures

Warning

Do not shake the patient

Shake the bottle well before use

Precautions

Storage conditions

Store in a cool place – not >0°C-8 °C is necessary for many products.

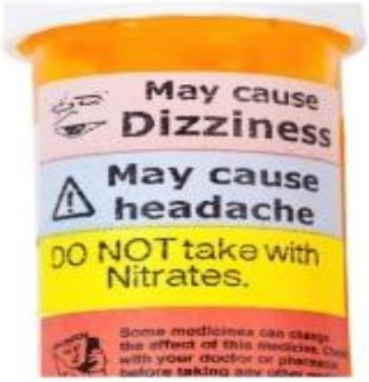
Protect from light

- Necessary for light sensitive preparations.
- Light resistive containers should be used.

Keep out of the reach of children

All dispensed medicines should carry this information on label.

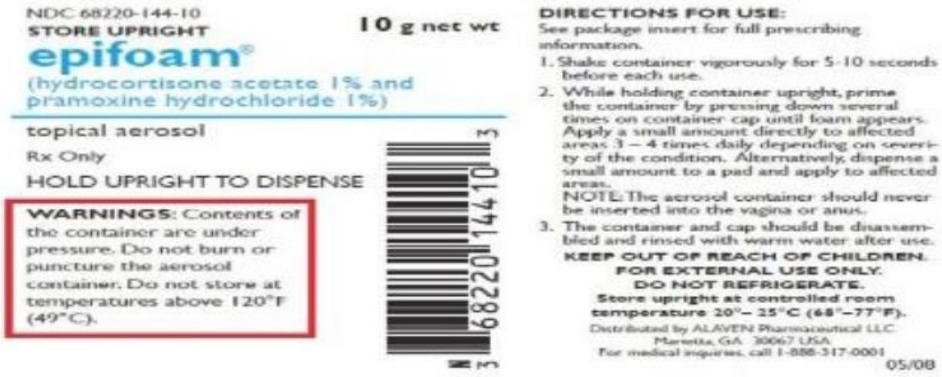
Warnings



For external use only

Inflammable

If the preparation contains 50% or more alcohol or any other inflammable solvent, then the label should contain the word inflammable.



Not to be taken

- Liquid preparation that are not administered by mouth
- For nasal drops, enemas and nasal sprays
- Unit dosage forms Eg: Pessaries and rectal suppositories
- Help to administer drugs safely
- Types of warning
    - If hypersensitivity to a drug
- For controlled substances

- About combining with other drugs or products

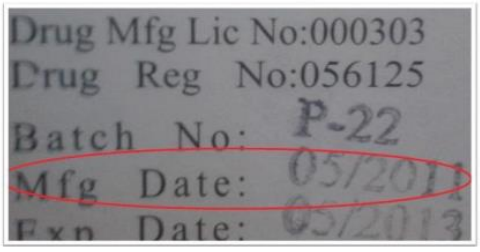
Registration number

A number given to a specific drug, when it is registered according to specific rules by registration board set up by federal government.

Batch number

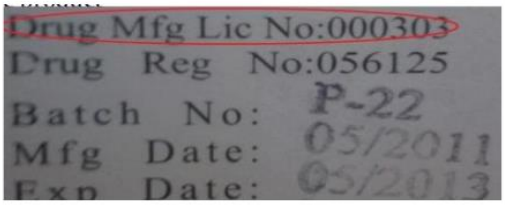
According to drug act 1976, "A designation printed on label of a drug that identifies the batch and permits the production history of the batch including all stages of manufacturer and control to be traced and are viewed"

Manufacturing date



Liscense number

Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The act requires a firm, who manufactures a biologic for sale in interstate commerce to hold a license for the product.

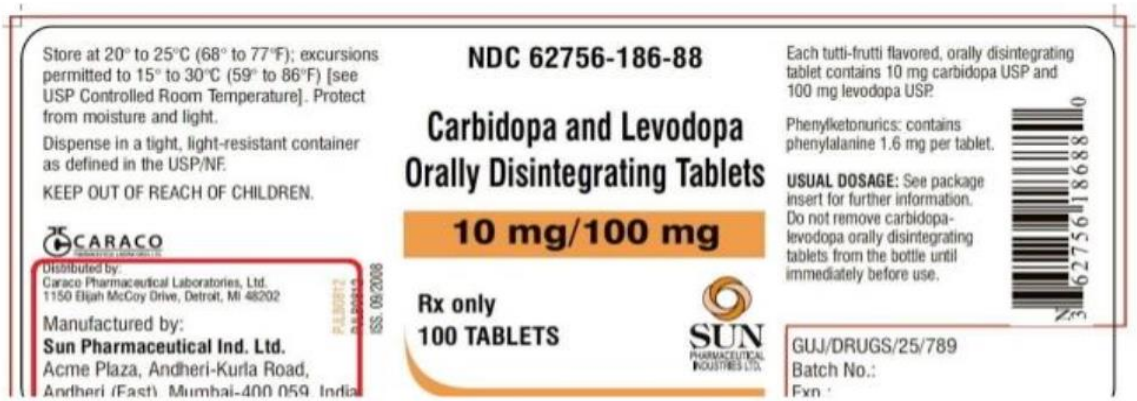


Expiry date

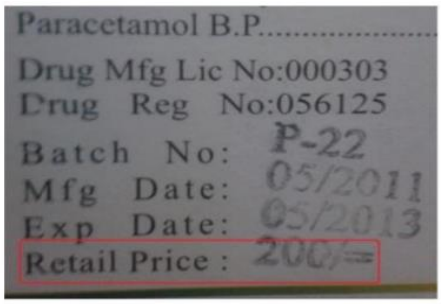
According to drug Act 1976 S3, "Date stated on the label of a drug after which a drug is not expected to retain its claimed efficacy, safety, quantity or potency or after which it is no permissible to sell the drug"

Manufacturer information

- Name
- Address

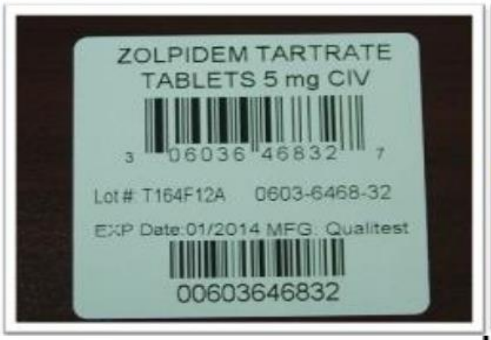


Price



Barcodes

It is an optical machine readable representation of data, which shows data about the object to which it attaches.

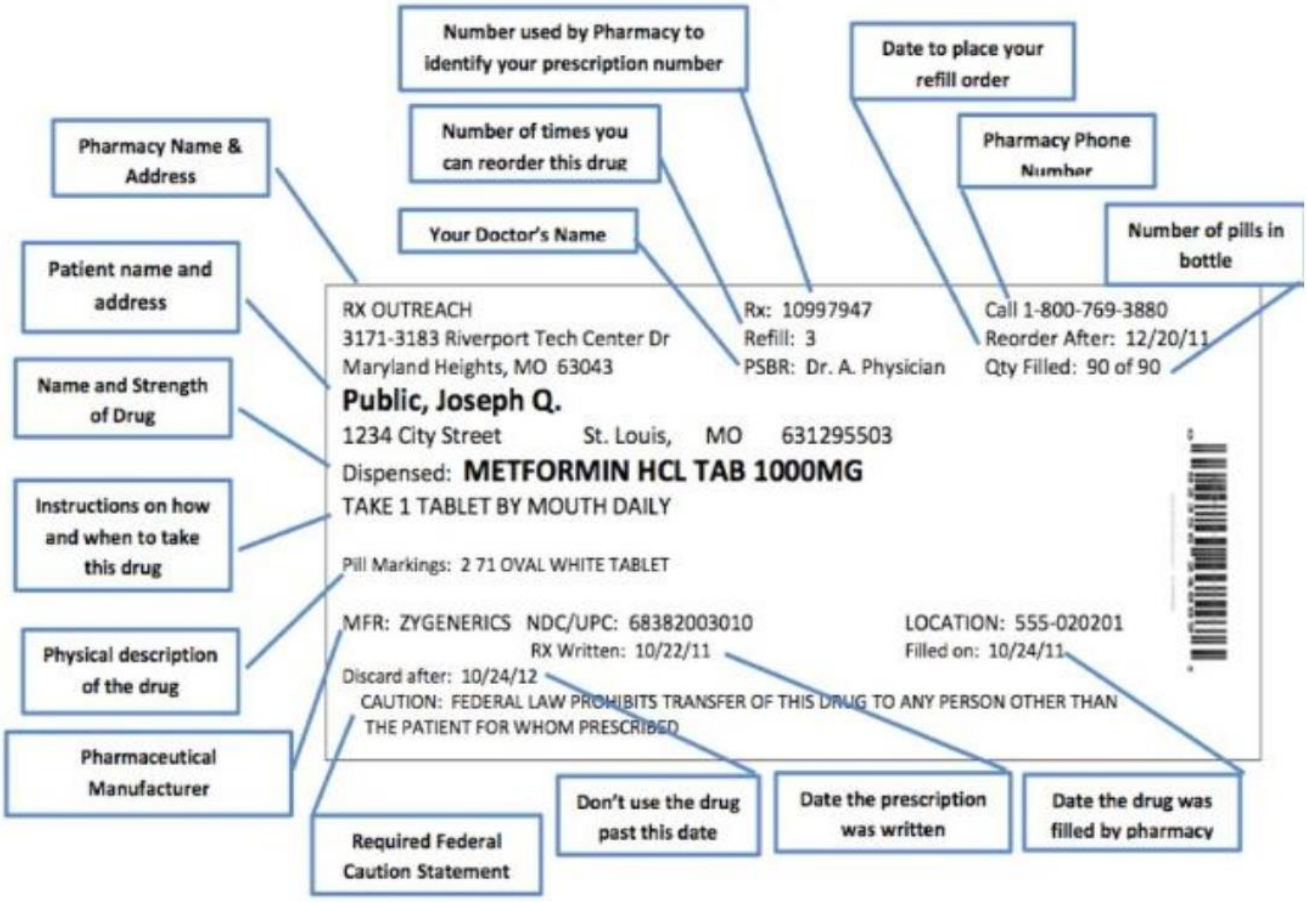


Dispensing label

It includes:

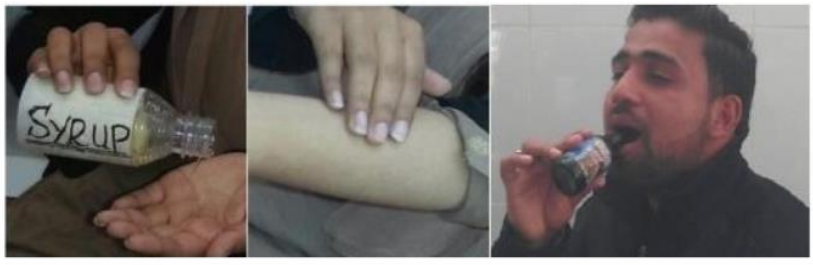
- Drug name and quantity

- Patient name
- Prescription number
- Phone number
- Instruction for use
- Pharmacy name and address



Special instructions

It includes the information about:



1. **Direction for use**

   How to take medicine

2. **Ear drops**

   For external use only

3. **Aerosols inhalations**

- Pressurized containers
- Keep away from heat source
- Shake before use
- Do not exceed the prescribed dose

4. **Creams**

For external use only

Store in cool place

Interactions

Certain drugs may have serious reactions if eat with particular food or drugs.

Eg: Amine containing foods (tyrosine) with monoamine oxidase inhibitors (Hypertension crises)

Tetracycline with milk

Packing Packing Techniques

Pharmaceutical packaging has to be carried out for the purpose of the safety of the pharmaceutical preparations in order to keep them free from contamination, hinder microbial growth, and ensure product safety through the intended shelf life for the pharmaceuticals. Packaging is a critical tool in the pharmaceutical industry.

Blister pack

- Blister pack is a term for several types of pre-formed plastic packaging used for small consumer goods, foods, and for pharmaceuticals.
- The primary component of a blister pack is a cavity or pocket made from a formable web, usually a thermoformed plastic. This usually has a backing of paperboard or a lidding seal of aluminum foil or plastic. A blister that folds onto itself is often called a clamshell.
- Blister packs are useful for protecting products against external factors, such as humidity and contamination for extended periods of time. Opaque blisters also protect light-sensitive products against UV rays.

Production Process

Thermoforming

In the case of thermoforming, a plastic film or sheet is unwound from the reel and guided though a pre-heating station on the blister line. The temperature of the pre-heating plates (upper and lower plates) is such that the plastic will soften and become pliable. The warm plastic will then arrive in a forming station where a large pressure (4 to 8 bar) will form the blister cavity into a negative mold.

The mold is cooled such that the plastic becomes rigid again and maintains its shape when removed from the mold. In case of difficult shapes, the warm film will be physically pushed down partially into the cavity by a "plug-assist" feature. Plug-assist results in a blister cavity with more uniform wall distribution and is typically used when the cavity size and shape is larger than a small tablets and capsules.

Cold forming

In the case of cold forming, an aluminum-based laminate film is simply pressed into a mold by means of a stamp. The aluminum will be elongated and maintain the formed shape. In the industry these blisters are called cold form foil (CFF) blisters. The principal advantage of cold form foil blisters is that the use of aluminum offers a near complete barrier for water and oxygen, allowing an extended

product expiry date. The principal disadvantages of cold form foil blisters are: the slower speed of production compared to thermoforming; the lack of transparency of the package (a therapy compliance disadvantage); and the larger size of the blister card (aluminum cannot be formed with near 90 degree angles).

Uses of blister pack

- Blister packs are commonly used as unit-dose packaging for pharmaceutical tablets, capsules or lozenges. Blister packs can provide barrier protection for shelf life requirements, and a degree of tamper resistance.
- In the US, blister packs are mainly used for packing physician samples of drug products, or for Over The Counter (OTC) products in the pharmacy. In other parts of the world, blister packs are the main packaging type since pharmacy dispensing and re-packaging are not common.
- A series of blister cavities is sometimes called a blister card or blister strip as well as blister pack. The difference between a strip pack and blister pack is that a strip pack does not have thermo-formed or cold formed cavities; the strip pack is formed around the tablet at a time when it is dropped to the sealing area between sealing moulds.
- In some parts of the world the pharmaceutical blister pack is known as a Push-Through-Pack (PTP), an accurate description of two key properties

  (i) the lidding foil is brittle making it possible to press the product out while breaking the lidding foil and

  (ii) a semi-rigid formed cavity being sufficiently collapsable to be able to dispense the tablet or capsule by means of pressing it out with the thumb.
- The main advantages of unit-dose blister packs over other methods of packing pharmaceutical products are the assurance of product/packaging integrity (including shelflife) of each individual dose and the ability to create a compliance pack or calendar pack by printing the days of the week above each dose.
- Blister packs are created by means of a form-fill-seal process at the pharmaceutical company or designated contract packer. A form-fill-seal process means that the blister pack is created from rolls of flat sheet or film, filled with the pharmaceutical product and closed (sealed) on the same

equipment. Such equipment is called a **blisterline.** There are two types of blister machine' design: rotary and flat-plate.

Clamshell

A clamshell is a one-piece container consisting of two halves joined by a hinge area which allows the structure to come together to close. Clamshells are often made of a shaped plastic material, in a way that is similar to a blister pack. The name of the clamshell is taken from the shell of a clam, which it resembles both in form and function.

Clamshell containers can be made of a variety of plastics such as polystyrene, polyester, PVC, foam sheets, etc. The material can by made by thermoforming or can be injection molded into the desired shapes. A single piece of material is used for the top and bottom with a "living hinge" that is integral with the material, rather than added separately.

Folding cartons made of paperboard or molded pulp can also be of a clamshell shape. It can also be made of cellulose fibersuch as sugarcane-bagasse, wheatstraw, wood pulp, etc.

Pill box

Paperboard Box containing tablets

A carton is a box or container usually made of paperboard and sometimes of corrugated fiberboard. Many types of cartons are used in packaging. Sometimes a carton is also called a box.

Eg: Carton box containing 1(PVC/AL) strip of 7 F.C tablets &an inner leaflet.

Cartons can be made from many materials: paperboard, duplex, white kraft, recycled and many more various plastics, or a composite. Some are "food grade" for direct contact with foods. Many cartons are made out of a single piece of paperboard. Depending on the need, this paperboard can be waxed or coated with polyethylene to form a moisture barrier. This may serve to contain a liquid product or keep a powder dry.

Ampoule

An **ampoule** is a small sealed vial which is used to contain and preserve a sample, usually a solid or liquid. Ampoules are commonly made of glass, although plastic ampoules do exist.

Modern ampoules are most commonly used to contain pharmaceuticals and chemicals that must be protected from air and contaminants. They are hermetically sealed by melting the thin top with an open flame, and usually opened by snapping off the neck. If properly done, this last operation creates a clean break without any extra glass shards or slivers; but the liquid or solution may be filtered for greater assurance. The space above the chemical may be filled with an inert gas before sealing. The walls of glass ampoules are usually sufficiently strong to be brought into a glovebox without any difficulty.

Glass ampoules are more expensive than bottles and other simple containers, but there are many situations where their superior imperviousness to gases and liquids and all-glass interior surface are worth the extra cost. Examples of chemicals sold in ampoules are:

- ✓ Injectable pharmaceuticals,
- ✓ Air-sensitive reagents like tetrakis (triphenylphosphine) palladium(0),
- ✓ Hygroscopic materials like deuterated solvents and trifluoromethanesulfonic acid, and
- ✓ Analytical standards.

Production

Modern glass ampoules are produced industrially from short lengths of glass tubing, shaped by heating with gas torches and gravity in automated production lines. Computer vision techniques are usually employed for quality control.

The filling and sealing of ampoules may be done by automated machinery on an industrial scale, or by hand in small-scale industries and laboratory settings. Blank ampoules can be purchased from scientific glass supply houses and sealed with a small gas torch. This forms a membrane allowing someone to turn the open ampule upside down without spilling. A **Schlenk line** may be used for sealing under inert atmospheres.

Ampoules often have colored rings of paint or enamel around their necks. Color

coding of modern ampoules is done during the manufacturing process. A machine paints colored rings on the ampoule shortly after it has been sealed. The rings are made of a substance that is readable by other machines. These color codes identify the substance inside the ampoule so that it does not need to be tested to verify the contents. The machine-readable color codes allow for accurate handling of the substance for the purposes of storage, labeling, and secondary packaging.

The dot above the neck identifies the location of a small cut in the glass to help breaking/opening the ampoule.

IV bags

About 25% of all plastic hospital products, including IV bags, are made of a plastic called polyvinyl chloride, or PVC. By itself, PVC is hard and brittle. But in the 1960s, manufacturers began adding chemicals called pthalates to make their products soft and flexible. Most IV bags contain a phthalate called DEHP (diethylhexyl phthalate).

Tubes for ointments, tooth paste, creams, lotion

A **tube** is a soft squeezable container which can be used for thick liquids such as adhesive, caulking, ointment, and toothpaste. Basically, a tube is a cylindrical, hollow piece with a round or oval profile, made of plastic, paperboard, or aluminum. Both ends of this tube are treated differently during the manufacturing process and filling. In general, on one end of the tube body there is a round orifice, which can be closed by different caps and closures. The orifice can be shaped in many different ways. Plastic nozzles in various styles and lengths are just one good example.

To attach caps and closures, in most cases a thread is tapped onto the opening structure. Furthermore, something all aluminium tubes have in common is that the other open end is folded several times after the contents have been added. The tube is thus hermetically sealed and nearly germ-free due to the high temperatures during the production process. Furthermore, it is possible to coat the inside of the tube with special coatings to prevent the material from reacting with the contents. Tubes are not poured from liquid aluminium; they are produced by the process of impact extrusion. In this process, the tube body is extruded from a small piece of aluminium with the round shape of a coin.

Unlimited printing designs can be applied to the tube, thanks to the wet-in-wet offset printing method. Six tones can be printed with this printing procedure, which gives packaging designers great opportunities to express their creativity.

The filled content can be easily squeezed out by the pressure of two fingers. The main characteristic of aluminium tubes is the total separation of the contents from the surrounding atmosphere; therefore, such tubes are especially suitable for the packaging of highly perishable contents. Aluminium tubes are used as packaging technology for cosmetics, pharmaceuticals, food, and technical products.

Plastic Tubes : Tube containers can also be produced in plastic, most commonly PE. The use of plastic tubes is very popular for the storage of Cosmetics such as hand creams etc. and also some food stuffs. The plastic tube retains its shape after each "squeeze" unlike laminate tubes such as toothpaste tubes. Plastic tubes can also be highly decorated or have a special additive such as soft touch to make the tube more appealing during use or point of sale (POS).

Plastic tubes are produced using the extrusion process. A "sleeve" is first produced using a very specialised extrusion line. The "Sleeve" must be produced to a very high standard (for decoration purposes) and also to very tight tolerances as automated processes are required post the extrusion operation. Once the "sleeve" is produced the tube head is fitted using an automated heading machine. Tube printing using complex and specialised printing machines such as silk screen printing applies the desired decoration. The open tubes are then most likely packed and despatched to another facility for filling and sealing.

Good manufacturing practices (GMP)

Good manufacturing practices (**GMP**) are the practices required in order to conform to the guidelines recommended by agencies that control authorization and licensing for manufacture and sale of food, drug products, and active pharmaceutical products. These guidelines provide minimum requirements that a pharmaceutical or a food product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public.

Good manufacturing practices, along with good agricultural practices, good laboratory practices and good clinical practices, are overseen by regulatory agencies in the United States, Canada, Europe, China, and other countries.

High level details

Good manufacturing practice guidelines provide guidance for manufacturing, testing, and quality assurance in order to ensure that a food or drug product is safe for human consumption. Many countries have legislated that food,and pharmaceutical and medical device manufacturers follow GMP procedures and create their own GMP guidelines that correspond with their legislation.

All guidelines follow a few basic principles:

- Manufacturing facilities must maintain a clean and hygienic manufacturing area.
- Controlled environmental conditions in order to prevent cross contamination of food or drug product from adulterants that may render the product unsafe for human consumption.
- Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
- Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.
- Instructions and procedures are written in clear and unambiguous language. (Good Documentation Practices)
- Operators are trained to carry out and document procedures.
- Cross contamination with unlabelled major allergens is prevented.
- Records are made, manually or by instruments, during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the food or drug was as expected. Deviations are investigated and documented.
- Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
- The distribution of the food or drugs minimizes any risk to their quality.
- A system is available for recalling any batch from sale or supply.
- Complaints about marketed products are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective products and to prevent recurrence.

Practices are recommended with the goal of safeguarding the health of consumers and patients as well as producing good quality food, medicine, medical devices, or active pharmaceutical products. In the United States, a food or drug may be deemed "adulterated" if it has passed all of the specifications tests, but is found to be manufactured in a facility or condition which violates or does not comply with current good manufacturing guideline. Therefore, complying with GMP is mandatory in all pharmaceutical manufacturing, and most food processing.

GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfil GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process.

The quality is built into the product and GMP is the most essential part of ensuring this product quality.

Guideline versions

GMPs are enforced in the United States by the U.S. Food and Drug Administration (FDA), under Title 21 CFR. The regulations use the phrase "current good manufacturing practices" (cGMP) to describe these guidelines. Courts may theoretically hold that a product is adulterated even if there is no specific regulatory requirement that was violated as long as the process was not performed according to industry standards. Since June 2010, a different set of cGMP requirements have applied to all manufacturers ofdietary supplements.

The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world. The European Union's GMP (EU-GMP) enforces similar requirements to WHO GMP, as does the FDA's version in the US. Similar GMPs are used in other countries, with Australia, Canada, Japan, Saudi Arabia, Singapore, Philippines, Vietnam and others having highly developed/sophisticated GMP

requirements. In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in what is commonly referred to as "The Orange Guide", which is named so because of the color of its cover; it is officially known as *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*.[2] Since the 1999 publication of *GMPs for Active Pharmaceutical Ingredients*, by the International Conference on Harmonization (ICH), GMPs now apply in those countries and trade groupings that are signatories to ICH (the EU, Japan and the U.S.), and applies in other countries (e.g., Australia, Canada, Singapore) which adopt ICH guidelines for the manufacture and testing of active raw materials.

GMC is part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization or product specification.

Enforcements

Within the European Union, GMP inspections are performed by National Regulatory Agencies (e.g., GMP inspections are performed in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA)); in the Republic of Korea (South Korea) by the Korea Food & Drug Administration (KFDA); in Australia by the Therapeutical Goods Administration (TGA); in Bangladesh by the Drug Administration (DGDA); in South Africa by the Medicines Control Council (MCC); in Brazil by the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil) (ANVISA); in Iran, in India gmp inspections are carried out by state FDA and these FDA report to Central Drugs Standard Control Organization [3] and Pakistan by the Drug Regulatory Authority of Pakistan;, Nigeria has NAFDAC and by similar national organisations worldwide. Each of theinspectorates carry out routine GMP inspections to ensure that drug products are produced safely and correctly; additionally, many countries perform pre-approval inspections (PAI) for GMP compliance prior to the approval of a new drug for marketing.

Regulatory agencies (including the FDA in the U.S. and regulatory agencies in many European nations) are authorized to conduct unannounced inspections, though some are scheduled. FDA routine domestic inspections are usually unannounced, but must be conducted according to 704(a) of the FD&C Act (21 USCS § 374), which requires that they are performed at a "reasonable time". Courts have held that any time the firm is open for business is a reasonable time for an inspection.