Current Good Manufacturing Practices and Current Good Compounding Practices

cGMP and cGCP

GMP

GMP regulations established by FDA to

- **Ensure that minimum standards present for drug product quality.**

- The cGMP regulations for:

bulk and **finished pharmaceutical products**).

c GMP REGULATIONS include

1. **Organization and Personnel**
2. **Personnel qualifications and Personnel responsibilities.**
3. **Buildings:** Design and Lighting, Ventilation, air filtration, air heating and cooling, Sanitation , Maintenance
4. **Equipment:** design, size, and location, Equipment construction, cleaning and maintenance.

1. **Filters**
2. **Containers and Closures**
3. Test drug: **approval or rejection of components**, **drug product containers, and closures**
4. Use of approved components, drug product containers, and closures
5. **Retesting of approved components**, drug product containers, and closures
6. **Rejected** components, drug product containers, and closures

F. **Production and Process Controls**: **Written procedures should present**.

1. Calculation of yield
2. Equipment identification
3. **Sampling and testing of in-process materials and drug products**

- **Active pharmaceutical ingredient (API):** Any component have pharmacologic activity in diagnosis, cure, mitigation, treatment or prevention of disease.
- **Batch:** **A specific quantity of a drug** of uniform specified quality produced according to single manufacturing order during the same cycle of manufacture.
- **Certification:** Documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed.
- **Compliance:** manufacturer acting with prescribed regulations, standards, and practices.

- **Component:** Any ingredient used in manufacture of drug product.
- **Drug product:** Finished form contains active drug and inactive ingredients.
- **Inactive ingredient:** Any component other than the active ingredients in drug product.
- **Lot:** A batch or any portion of a batch having uniform specified quality and a distinctive identifying lot number.
- **Lot number, control number, or batch number:** combination of letters, numbers, or symbols from which the complete history of manufacture, processing, packaging, holding, and distribution of a batch or lot of a drug product may be determined.

- **Master record:** **Record containing the formulation**, specifications, manufacturing procedures, quality assurance requirements, and labeling of finished product.
- **Quality assurance:** all evidence needed that activities relating to quality are being performed adequately.
- **Quality control:** process through which industry measures actual quality performance, compares it with standards.

- **Quality control unit:** organizational element designated by a firm to be responsible for work related to quality control.

- **Quarantine:** An area that is marked, designated, or set aside for the holding **of incoming components** **prior to acceptance testing** and qualification for use.

- **Representative sample:** A sample that represent the whole product.
- **Reprocessing:** **recycling:**The activity that finished product or any of its components is recycled through all or part of the manufacturing process.
- **Strength:** concentration of drug per unit dose or volume.
- **Verified:** Signed by a second individual or recorded by automated equipment.
- **Validation:** Documented evidence that a system (e.g., equipment, software, controls) does what it purpots to do.
- Process validation: Documented evidence that a process (e.g., sterilization) does what it purports to do.
- Validation protocol: experimental plan to produce documented evidence that the system has been validated.

Organization and personnel

- deals with responsibilities of quality control unit, employees, and consultants.
- quality control unit have responsibility for all functions that affect product quality. This includes **accepting** or **rejecting** product components, product specifications, finished products, packaging, and labeling. Adequate laboratory facilities shall be provided, written procedures followed, and all records maintained.
- All personnel required to have **education, training, and experience**
- Appropriate programs of education and training, and performance evaluations are essential for maintaining quality assurance.

EQUIPMENT

- Each piece of equipment must be :**appropriate design** and **size** to facilitate **use, cleaning, and maintenance**.
- equipment's surfaces and parts **must not interact** with processes or product s so not affect **purity, strength**, or **quality.**
- Standard operating **procedures must be written** and followed for proper use, maintenance, and cleaning of each piece of equipment.
- equipment and computers used in the processes must be **routinely calibrated**, maintained, and validated for accuracy.
- Filters used in the manufacture or processing of injectable drug products **must not** release fibers into such products.

Control of componants, containers and closure

- Written procedures, identification, storage, handling, sampling, testing, and **approval or rejection** of all product components, containers, and closures must be maintained and followed.
- Bulk pharmaceutical chemicals, containers, and closures must meet the required property.
- Raw materials should verified through sampling and qualitative and quantitative analysis.
- **Rejected components**, containers, and closures are identified and controlled under a **quarantine system** to prevent their use in manufacturing and processing operations.

- Mainly bulk chemicals (APIs) are synthesized in **China and India**
- it is important to confirm their identity and purity with **USP** and **NF** prior to use in finished pharmaceuticals.

PRODUCTION AND PROCESS CONTROLS

- **Written procedures** are required to ensure that drug products have correct **identity**, **strength**, **quality**, and **purity**.

- In-process samples taken from production batches periodically for product control.

Packaging and labeling control

- Written procedures are required for the receipt, identification, storage, handling, sampling, and testing of drug product and issuance of labeling and packaging materials.
- **Expiration Dating**

Expiration Dating

- To ensure that a drug product meets standards of identity, strength, quality, and purity at time of use.

- Except from this requirement are **homeopathic drug products**, **allergenic extracts**, and investigational drugs that meet the standards established during preclinical and clinical studies.

HOLDING AND DISTRIBUTION

- Written procedures must be established and followed for the holding and distribution of product.
- Finished pharmaceuticals must be quarantined in storage until released by the quality control unit.
- Products must be stored and **shipped** under conditions that **do not affect product quality.**
- the oldest approved stock is distributed first.
- The distribution control system must allow the distribution point of each lot of drug product to be readily determined to facilitate its recall if necessary.

LABORATORY CONTROLS

- Laboratory controls are requirements for the establishment of and conformance to :
- **written specifications**,
- **standards**,
- **sampling plans**,
- **test procedures**.
- The specifications, which apply to each batch of drug product, include **sample size**
- **test intervals**
- **sample storage**
- **stability testing**

special testing requirements for parenterals, ophthalmics , controlled-release products, and radioactive pharmaceuticals.

Complete master production and control records for each batch must be kept and include the following:

- Name and strength of the product
- Dosage form
- Quantitative amounts of components.
- Complete manufacturing and control procedures
- Equipment used
- In-process controls
- Sampling and laboratory methods and assay results
- Calibration of instruments
- Distribution records
- Dated and employee-identified records

ADDITIONAL cGMP REQUIREMENTS

Active Pharmaceutical Ingredients and Exciepients

The quality of any finished product depends on the quality of the components, and active ingredients.

GMP focuses on all elements of chemical purity and quality, including following:

- **Specifications and analytical methods for all reactive and nonreactive components** used.
- chemical reaction steps
- Handling of chemical intermediates
- Quality of water used.
- Solvent handling and recovery systems
- Analytical methods to detect impurities or chemical residues and limits set
- Stability studies of bulk pharmaceutical chemical

MEDICAL DEVICES

1. devices are approved for marketing when shown to be safe and effective through premarket approval.
2. Medical devices are subject to the reporting of adverse events, to recall, and to termination of approval.
3. The regulations for "good manufacturing practice for medical devices" are similar to those for finished pharmaceuticals. They include **personnel**; **buildings**; **equipment**; **control of components**; production and process controls; packaging and labeling; holding, distribution, and installation; device evaluation; and records.

- Devices covered by cGMP regulations include:

1. **intraocular lenses,**
2. **hearing aids,**
3. **intrauterine devices,**
4. **cardiac pacemakers,**
5. **clinical chemistry analyzers,**
6. **catheters,**
7. **cardiopulmonary bypass heart-lung machine console,**
8. **dental X-ray equipment,**
9. **surgical gloves,**
10. **prosthetic hip joints,**
11. **traction equipment,**
12. **computed tomography equipment, and**
13. **powered wheelchairs.**

USP-NF FORMULARY

- In the **absence of stability information**, the following maximum time use after opening are recommended for **non sterile** compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature:

1. For **non aqueous liquids and solid** formulations:

(a) Where manufactured drug product is the source of active ingredient, the beyond-use date is **not later than 25%** of the time remaining until the product's expiration date or 6 months.

(b) where a USP or NF substance is the source of active ingredient, the beyond-use date is not later than 6 months.

- For water-containing formulations prepared from ingredients in solid form, the beyond-use date is not later than **14 days** when stored at cold temperatures.

- For all other formulations, use date is not later than intended duration of therapy or **30 days**.
- **If no sterility testing program is in place, the following apply:**

1. For low-risk preparations at room temperature use dates not more than **48 hours** and for refrigerated temperatures, not more than **14 days**.
2. For medium-risk preparations at room temperature, use **not more than 30 hours** and for **refrigerated temperatures, not more than 9 days.**
3. For high-risk preparations at room temperature, **not more than 24 hours** and for **refrigerated temperatures, not more than 3 days.**

In all three instances, if stored at -25°C to -10°C, the beyond-use dates are 45 days in the solid state.

CONTAINERS

- must **provide adequate drug stability**.

qualities tested for containers

1. Physicochemical properties.
2. Light-transmission for glass or plastic.
3. Drug compatibility.
4. Leaching and/or migration.
5. Vapor transmission for plastics.
6. Moisture barrier.
7. Toxicity for plastics.
8. Valve, actuator, metered dose, particle size, spray characteristics, and leaks for aerosols.
9. Sterility and permeation for parenteral containers.
10. Drug stability for all packaging.

- According to USP, a **container is** “that which **holds the article** and is **or in direct contact with article**.” The immediate container is “that which is in direct contact with the article at all times.”
- The closure is part of the container.

- The container, should be **clean and dry** before it is filled with drug.
- must not interact physically or chemically with the drug.

- Ex:sorption of diazepam, to low density plastics resulting in a loss of drug avoided with the use of glass containers.

The USP classifies containers according to their ability to protect their contents from external conditions.

1. **well-closed container**. "protects contents from solids and from loss under ordinary conditions of handling, shipment, storage, and distribution."
2. **A tight container** "protects contents from contamination by liquids, solids, or vapors, or evaporation under the ordinary conditions of handling, shipment, storage, and distribution and is capable of tight re-closure."

3. **A hermetic container** "is impervious to air or any other gas under the ordinary conditions of handling, shipment, storage, and distribution."

4. **Sterile hermetic containers** hold preparations intended for injection or parenteral administration.

- **A single-dose container :**when opened, cannot be resealed with assurance that sterility has been maintained.
- These containers include **fusion sealed ampoules** and **prefilled syringes and cartridges**.

- **A multiple-dose container** is a **hermetic container** that permits withdrawal of successive portions of the contents without changing the strength or affect the quality or purity of the remaining portion. These containers are commonly called **vials**.

- **unit dose package:** positive identification of each dosage unit and **reduction of errors**, **reduced contamination** of the drug.
- packaging materials may be combinations of paper, foil, plastic, or cellophane.

Oral liquids

- dispensed in single units in paper, plastic, or foil cups or prepackaged and dispensed in glass containers having threaded caps or crimped aluminum caps.
- disposable plastic oral syringes with rubber or plastic tips on the orifice for closure.

- suppositories, powders, ointments, creams, and ophthalmic solutions, are also commonly found in single-unit packages.

unit-of-use packaging

- the quantity of drug product prescribed is packaged in a container.

- Ex: if certain antibiotic capsules are prescribed to be taken 4 times a day for 10 days, unit-of-use packaging would contain 40 capsules. Other products may be packaged to contain a month's supply.

light-resistant containers

- **Amber glass** or a light-resistant **opaque plastic** will reduce light transmission sufficiently to protect a **light-sensitive** pharmaceutical.
- **ultraviolet absorbers** may be added to plastic to decrease the transmission of short ultraviolet rays.
- USP standards that define the acceptable limits of light transmission at any wavelength between 290 and 450 nm.

- recent innovation in plastic packaging is the **coextruded two-layer high-density polyethylene bottle**, which has an **inner layer** of **black polyethylene coextruded** with an **outer** layer of **white polyethylene**. The container provides:

1. **light resistance.**
2. **moisture protection**.

Increasingly being used in packaging of tablets and capsules.

Glass used in packaging pharmaceuticals

- 4 categories :
- **Types I, II, and III** intended for **parenteral products**, and type**IV: NP** is intended for other products.
- Each type tested according to resistance to water attack.
- Degree of attack is determined by **amount of alkali released** from glass in specified test conditions.
- leaching of alkali from glass to preparation could alter

1. pH
2. Stability of product.

- Type I is most resistant glass of 4 categories.

- **Today**, most products are packaged in **plastic**.
- intravenous fluids, plastic ointment tubes, plastic film-protected suppositories, and plastic tablet and capsule vial.

- **Advantage over glass:**

1. **Light** and resistance to impact, which reduces costs and losses due to container damage
2. Versatility in container design, consumer acceptance
3. Consumer preference for plastic squeeze bottles in administration of ophthalmics, nasal sprays, and lotions
4. The popularity of blister packaging and unit-dose dispensing.

- **Example**, Addition of **methyl groups** to every other carbon atom in the polymer chains of **polyethylene** will give **polypropylene**, material that can be **autoclaved**.
- If a **chlorine** atom is added to every other carbon in the **polyethylene** polymer, **polyvinyl chloride** (PVC) is produced. This material is **rigid and has good clarity**, making it particularly useful in the **blister packaging** of tablets and capsules. However, it has a significant drawback for packaging medical devices (e.g., syringes): it is **unsuitable for gamma sterilization**, a method that is being used increasingly.

- The placement of other functional groups on the main chain of **polyethylene** or added to polymers can give a variety of alterations to final plastic material. Among the newer plastics are **polyethylene terephthalate** (PET), **amorphous polyethylene terephthalate** glycol (APET), and polyethylene terephthalate glycol (PETG). Both APET and PETG have excellent **transparency** and can be **sterilized with gamma radiation**.

- Among **problems** encountered in the use of **plastics** in packaging are:
- (a) **Permeability of containers to atmospheric oxygen and moisture vapor.**
- (b) **Leaching of constituents of to the internal contents.**
- (c) **Absorption of drugs from contents to container.**
- (d) **transmission of light through container**.
- (e) **Alteration of container upon storage**.
- **plasticizers, stabilizers, antioxidants, antistatic agents, antifungal agents, colorants, and others.**

- The permeability of a plastic is a function of:

1. Nature of polymer;
2. the amounts and types of plasticizers,
3. fillers, lubricants, pigments and other additives;
4. pressure; and temperature.

- Increases in temperature, pressure, and the use of additives tend to increase permeability of plastic. Glass containers are less permeable than plastic containers.

- Many products liable to deteriorate in humidity unless protected by high-barrier packaging.
- Desiccant silica gel in small packets, commonly included as protection against effects of moisture vapor.
- Drug substances that are subject to **oxidative degradation** may undergo a greater degree of degradation when packaged in plastic than in glass.
- Liquid in plastic may **lose drug molecules** or solvent to the container, altering the concentration of drug in product and affecting its potency.

- **Leaching** is term used to describe **movement of components of container to contents**.
- Compounds leached: polymer additives, such as the plasticizers, stabilizers, or antioxidants. **The leaching occurs when liquids or semisolids are packaged in plastic.** Little leaching occurs when tablets or capsules are packaged in plastic.
- influenced by temperature, agitation

- **Sorption** indicate **binding of molecules to polymer** includes both **adsorption and absorption**.
- Sorption occurs through chemical or physical means.
- **un-ionized species of solute has greater tendency to bound than ionized species.**
- degree of ionization of a solute affected by pH of solution, the pH may influence sorption of particular solute.
- **Plastic materials with polar groups are prone to sorption.** Because **sorption depends on penetration or diffusion of a solute into plastic.**

- **Sorption** may occur with **active pharmacologic agents** or **with excipients**.
- Sorption may be initiated by the **adsorption of a solute to the inner surface of a plastic container.**
- After saturation of the surface, the solute may diffuse into the container and bound within plastic.
- The sorption of excipients :colorants, preservatives, or stabilizers would likewise alter the quality of product.
- Methylparaben may be sorbed to some types of plastics, resulting in a decrease in the available concentration of preservative.

- Deformations, softening, hardening, and other physical changes in plastic containers can be caused by the action of container's contents or external factors, including changes in temperature and physical stress placed upon the container in handling and shipping.

Child-Resistant & Adult-Senior use Packaging

- Defined as one that is significantly difficult for children under 5 years of age to open or to obtain a harmful amount of its contents within a reasonable time and that is not difficult for “normal adults” to use properly.

Compliance packaging

- blister packaging in a calendar pack.
- These medication compliance useful for :**patients taking multiple medications.**

LABELING

- company literature
- advertising and promotional material
- booklets, mailing pieces, file cards, price lists, catalogs, sound recordings, film strips, motion picture films, slides, exhibits, displays, literature reprints, and computer-accessed information; and other materials related to the product.
- Important information for a prescription-only drug.

MANUFACTURER'S LABEL

- The nonproprietary name of drug or The name of the manufacturer, packer, or distributor of the product.
- A quantitative statement of the amount of each drug per unit of weight, volume, or dosage unit.
- The pharmaceutical type of dosage form constituting the product
- The net amount of drug product contained in the package, in units of weight, volume, or number of dosage units, as appropriate
- The logo "Rx only" or the federal legend "Caution—Federal law prohibits dispensing without prescription" or a similar statement.
- A label reference to refer to the accompanying package insert or other product literature for dosage and other information.
- Special storage instructions when applicable.
- The National Drug Code identification number for the product (and often a bar code)
- An identifying lot or control number.
- An expiration date.
- "Warning—May be habit forming" may also appear.

PRESCRIPTION LABEL

- **Name and address of the pharmacy**
- Serial number of prescription
- Date of the prescription or the date of its filling or refilling (state law often determines which date is to be used).
- Name of prescriber
- Name of patient
- Directions for use, include any precautions, as indicated on prescription.

1. The address of the patient
2. The initials or name of the dispensing pharmacist
3. The telephone number of the pharmacy
4. The drug name, strength, and manufacturer's lot or control number
5. The expiration date of the drug
6. The name of the manufacturer or distributor
7. In an effort to decrease medication errors, there is thought to include the “indication” on the prescription label to help the pharmacist assure the prescribed drug is appropriate.

OVER-THE-COUNTER LABELING

- Product name.
- Name and address of manufacturer, packer or distributor.
- Quantity of contents.
- Names and quantities of all active ingredients /dosage unit. Inactive ingredients also listed.
- Name of any habit-forming substance or substances in the preparation.
- Statement of pharmacologic category (e.g., antacid) and adequate directions for safe and effective use, for example, dose, frequency of dose, dose and age considerations, route of administration, and preparation for use, such as shaking or dilution.

- Cautions and warnings.
- Sodium content for certain oral products intended for ingestion, when the product contains 5 mg of sodium or more/single dose or 140 mg or more in maximum daily dose.
- Storage conditions.
- Lot number and expiration date.

- geriatric patients, might be unable to read a label physically, easy-to-read font size is required along with other graphical features that promote the ability to read the label information.

Dietary Supplement Labeling

- Should write: "**improve mood**" rather than treat depression
- Should write :**This product is not intended to diagnose, treat, cure, or prevent any disease**."
- For herbal products, the label must also state **the part of the plant used to make the product**, for example, root, stem, leaf.
- minimum information about the product prior to its use.

STORAGE

- product must be stored in proper conditions.
- The labeling of product includes **the desired conditions of storage.**
- **Cold:** Any temperature not exceeding **8°C.**
- A **refrigerator** is a cold place in which the temperature is maintained thermostatically between **2° and 8°C**.
- **A freezer** is a cold place in which the temperature is maintained thermostatically **between -25° and -10°C.**
- **Cool:** Any temperature between **8° and 15°C**.

- **Room temperature:** The temperature in a working area. 20° to 25°C.
- **Warm:** Any temperature between **30° and 40°**C.
- **Excessive heat**: **Above 40°**C.
- Protection from freezing: in addition to the **risk of breakage** of container, freezing subjects a product to **loss of strength** or **potency** or to **destructionof dosage form**.
- TRANSPORTATION
- The stability protection of a pharmaceutical product during transportation is important.