GMP AND cGMP CONSIDERATIONS

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- cGMP refers to the Current Good Manufacturing Practice regulations enforced by the US Food and Drug Administration (FDA).
- cGMP provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations.
- This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.
- This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors.
- This assures that drug products meet their quality standards.

➢ *TRAGEDIES PREECEDING CGMP REGULATIONS*

- 1902 - Development of the Biologic Control Act
- 1906 - Development of the Pure Food and Drug Act
- 1938 - Federal Food, Drug and Cosmetic Act
- 1941 - Initiation of GMP
- 1944 - Development of Public Health Services Act
- 1962 - Kefauver-Harris Drug Amendments released (It introduced a requirement for drug manufacturers to provide proof of the effectiveness and safety of their drugs before approval, required drug advertising to disclose accurate information about side effects, and stopped cheap generic drugs being marketed as expensive drugs under new trade names as new "breakthrough medications)
- 1963 - Establishment of GMPs for Drugs
- 1975 - cGMP for Blood and Components Final Rule
- 1976 - Medical Device Amendments
- 1978 - cGMP for Drugs and Medical Devices

- 1979 - GLPs Final Rule
- 1980 - Infant Formula Act is passed
- Sulfathiazole tablets contaminated with phenobarbital
- 1941 - 300 people died/injured
- FDA to enforce and revise manufacturing and quality control requirements
- 1941 - GMP is born
- Thalidomide tragedy
- Thousands of children born with birth defects due to adverse drug reactions of morning sickness pill taken by mothers
- Strengthen FDA’s regulations regarding experimentation on humans and proposed new way how drugs are approved
- and regulated
- “Proof of efficacy” law

What are cGMPs

- Regulations are established by the Food and Drug Administration **(FDA) to ensure that minimum standards are met for drug product quality in the United States.**

OR

- Rules set up by the FDA that drug manufacturers needs to follow in order to ensure that a **safe and effective product is manufactured**

➢ *COMPONENTS OF cGMP*

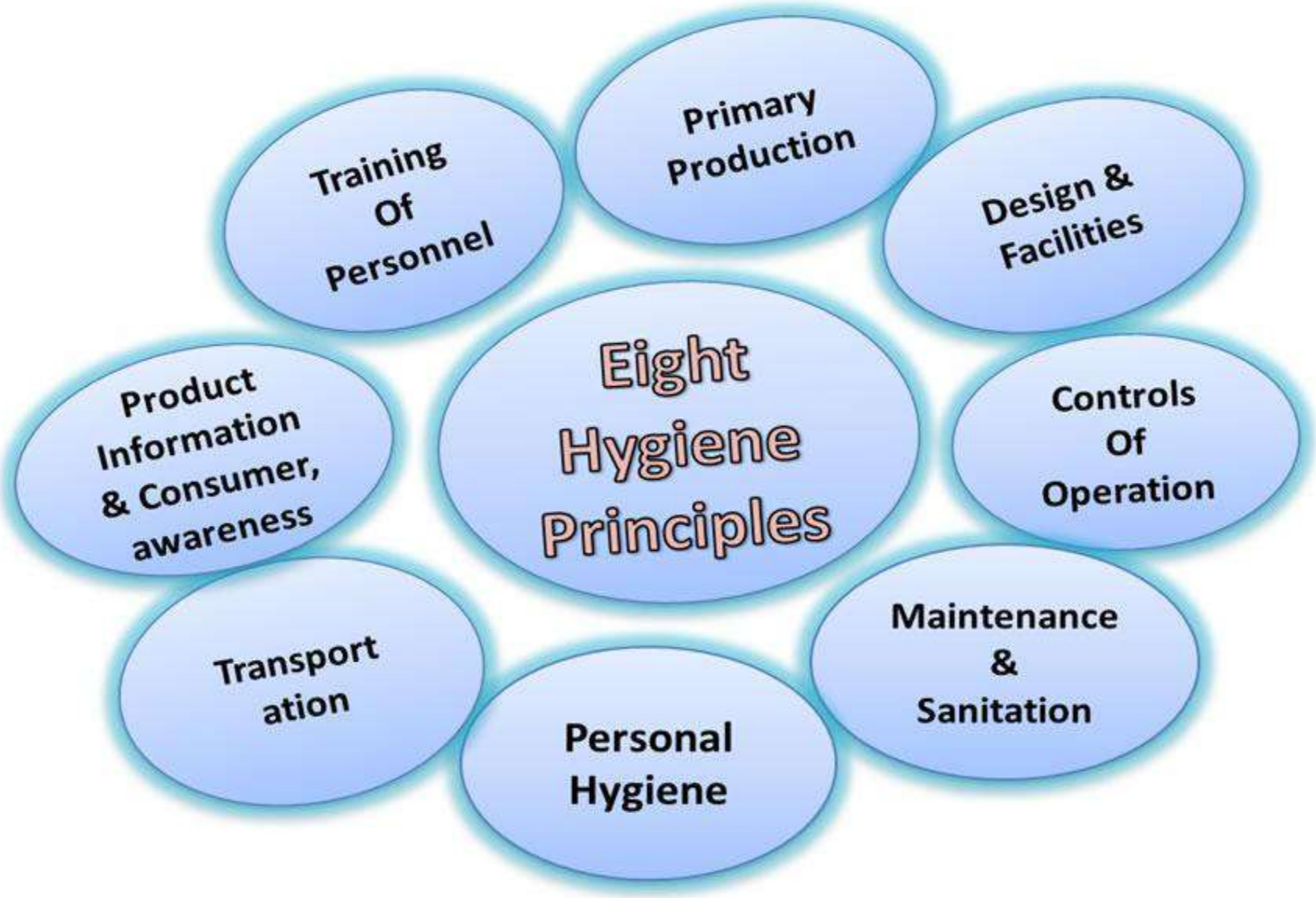
- a) GMP is a part of Q.A
- b) GMP's main function is to produce quality products consistently.
- c) GMP must meet legal requirements of country.
- d) GMP must meet both production and Q.C. related issues.
- e) WHO further comments that the main function of GMP is to avoid mix-ups and contamination risks.

- ***cGMP COVERS***
- a) General considerations
- b) Personnel
- c) Premises
- d) Equipment
- e) Sanitation
- f) SOP’s
- g) Raw Materials
- h) Self Inspection And Audit
- i) Master Formula Records
- j) Batch Manufacturing Records
- k) Warehousing Area
- l) Labels And Other Printed Materials
- m) QA

cGMP For Finished Pharmaceuticals

- **General Provision**
- **Organization & Personnel**
- **Building & Facilities**
- **Equipment**
- **Control of Components & Drug**
- **Product Containers & Closures**
- **Production & Process Control**
- **Packaging & Labeling Control**
- **Handling & Distribution**
- **Laboratory Control**
- **Records & Reports**
- **Returned & Salvaged Drugs**

GMP


Eight Hygiene Principles
Primary Production
Design & Facilities
Controls Of Operation
Maintenance & Sanitation
Personal Hygiene
Transport ation
Product Information & Consumer, awareness
Training Of Personnel

GMP

CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

The GMP Institute was established Ten Principles of cGMP

- **Principle1:** Writing detailed step-by-step procedures that provide a roadmap for controlled and consistent performance
- **Principle2 :**Carefully following written procedures to prevent contamination, mix-ups and errors.

Importance of Written Procedures:
Procedures should be Clear , Concise and Logical

Importance of Written Procedures
Taking shortcuts may save time or make the task easier, but you **should never deviate from a written procedure without the approval of a supervisor or Quality Department**

- **Principle3 :** Promptly and accurately documenting work for compliance and traceability
- **Principle 4:** Proving that systems do what they are designed to do by validating

Validate and Document Work:
To prove that our equipment and process consistently do what they are supposed to do

Principle 5 : Develop a good design for the facility and the equipment from the beginning

Principle 6 : Properly maintaining facilities and equipment

Design , construction and maintenance of the facility and equipment

A Logical and well planning layout will improve productivity.

Remove unnecessary traffic in the production area

Segregate materials , products, and their components to minimize the confusion and potential mix-ups and errors

It is important to control :

Air, Water, Lighting, Ventilation, Temperature and RH

- **Principle7 :** Clearly defining, developing and demonstrating job competence

GMP makes for Competent Employees

Training: include basic training on the theory and practice of GMP as well as specific training relative to their role .

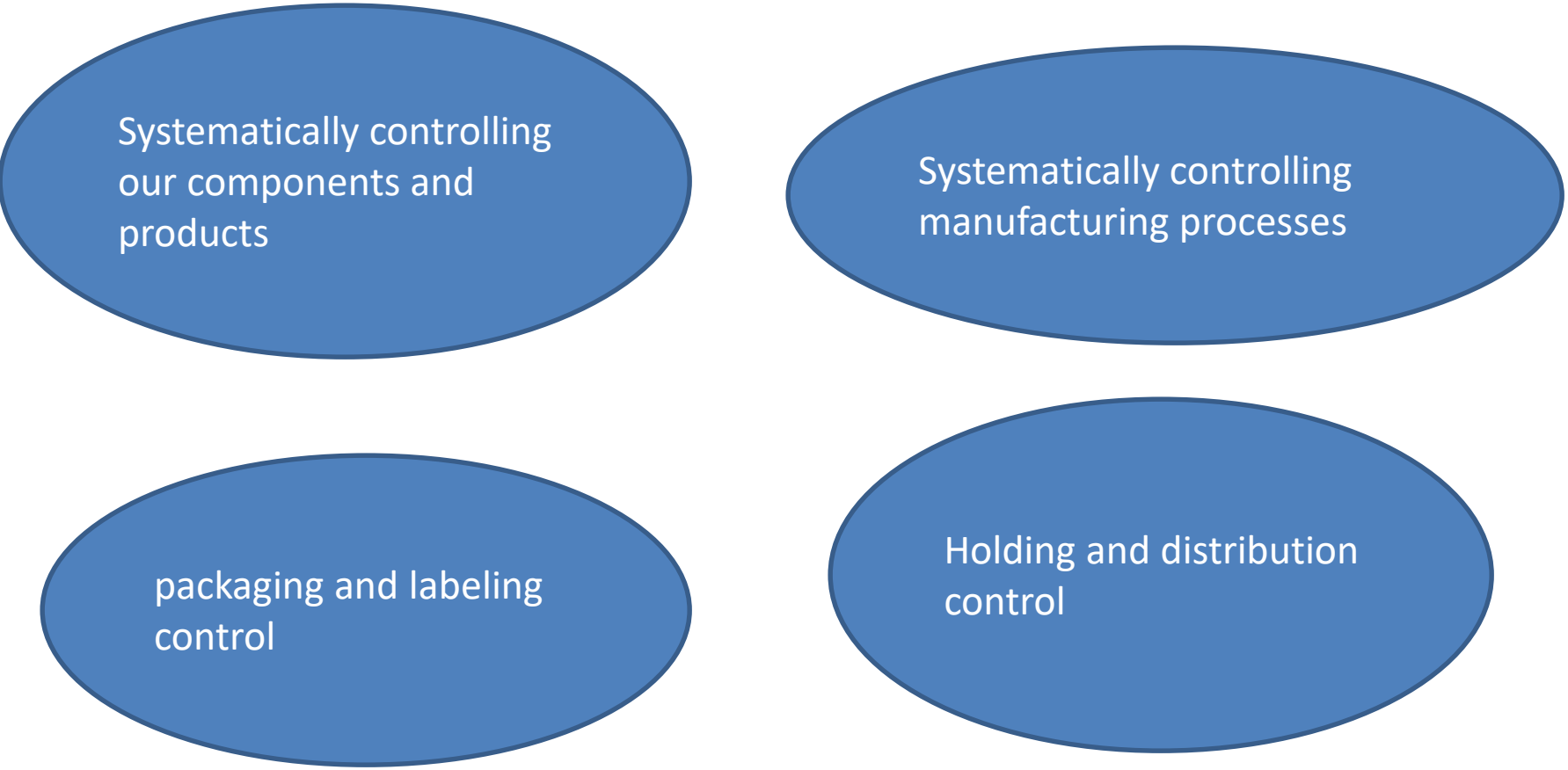
Companies need people who know to do the job right the first time , every time

Principle 8 : Protecting products against contamination by making cleanliness a continual habit.

Practice good Hygiene

- Health examinations
- *Written procedures and instructions - to wash hands before entering production areas*
- Direct contact between product, raw materials and operator *Should be avoided*
- Protection of product from contamination:
  - *Clean clothes appropriate to personnel activities*
  - *Including hair covering (e.g. caps)*
- Check change rooms/changing facilities
- Smoking, eating and drinking not allowed in production areas, laboratories and storage areas
- No chewing (e.g. gum), or keeping food or drinks allowed
- No plants kept inside these areas
- Rest and refreshment areas should be separate from manufacturing and control areas

Principle 9: Building quality into products by.



Principle 10 : Conducting planned and periodic audits for compliance and performance**.**

- **CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS**
- **Subpart A--**General Provisions
- **Subpart B--**Organization and Personnel
- **Subpart C--**Buildings and Facilities
- **Subpart D—**Equipment
- **Subpart E--**Control of Components and Drug Product Containers and Closures
- **Subpart F--**Production and Process Controls

- **Subpart G--**Packaging and Labeling Control
- **Subpart H--**Holding and Distribution
- **Subpart I--**Laboratory Controls
- **Subpart J--**Records and Reports
- **Subpart K--**Returned and Salvaged Drug Products

Active ingredient or active pharmaceutical ingredient (API): Any component that is intended to furnish pharmacologic activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body of man or other animals.

- **Batch:** A specific quantity of a drug of uniform specified quality produced according to a single manufacturing order during the same cycle of manufacture
- **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:** Any distinctive combination of letters, numbers, or symbols from which the complete history of the manufacture, processing, packaging, holding, and distribution of a batch or lot of a drug product may be determined.

- **Certification:** Documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are acceptable.
- **Compliance:** Determination through inspection of the extent to which a manufacturer is acting in accordance with prescribed regulations, standards, and practices.
- **Component:** Any ingredient used in the manufacture of a drug product, including those that may not be present in the finished product.
- **Inactive ingredient:** Any component other than the active ingredients in a drug product
- **Drug product:** A finished form that contains an active drug and inactive ingredients. The term may also include a form that does not contain an active ingredient, such as a placebo.

- **Master record:** Record containing the formulation, specifications, manufacturing procedures, quality assurance requirements, and labeling of a finished product .

- **Quality assurance:** Provision to all concerned the evidence needed to establish confidence that the activities relating to quality are being performed adequately.
- **Quality audit:** A documented activity performed in accordance with established procedures on a planned and periodic basis to verify compliance with the procedures to ensure quality.

- **Quality control:** The regulatory process through which industry measures actual quality performance, compares it with standards, and acts on the difference.

- **Quality control unit:** An organizational element designated by a firm to be responsible for the duties relating to quality control

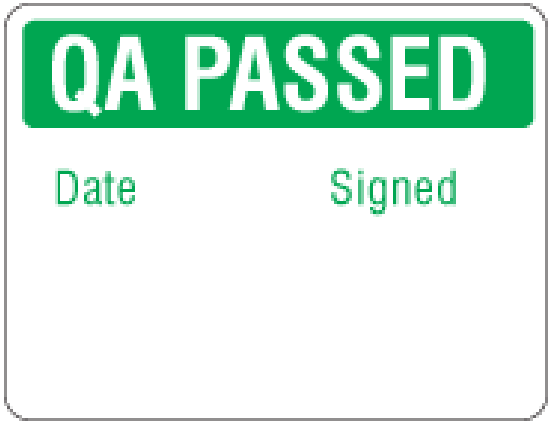
- **Quarantine:** An area that is marked, designated, or set aside for the holding of incoming components prior to acceptance testing and qualification for use.
- **Reprocessing:** The activity whereby the finished product or any of its components is recycled through all or part of the manufacturing process.
- **Strength:** The concentration of the drug substance per unit dose or volume

Subpart A--General Provisions

- The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs) for administration to humans or animals.

Subpart B--Organization and Personnel

- Responsibilities of quality control unit.
- Personnel qualifications.
- Personnel responsibilities.
- Consultants.



Responsibilities of quality control unit.

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

- **Personnel qualifications.**

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions.

(b) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

Personnel responsibilities.

(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

(b) Personnel shall practice good sanitation and health habits.

(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

- **Consultants.**

  Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained

- **Subpart C--**Buildings and Facilities:
- Design and construction features.
- Any building or buildings used in the manufacture, processing, packing, or holding of a drug product
- shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
- shall have adequate space

➢ Lighting.
➢ Ventilation, air filtration, air heating and cooling.
➢ Plumbing.
➢ Sewage and refuse.
➢ Washing and toilet facilities.
➢ Sanitation.
➢ Maintenance.

- **Subpart D—Equipment - Equipment design, size, and location. - Equipment construction.** Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product

Equipment cleaning and maintenance. Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product **- Automatic, mechanical, and electronic equipment.**

Filters.

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products.

- **Subpart E--Control of Components and Drug:**

-Receipt and storage of untested components, drug product containers, and closures.

-Testing and approval or rejection of components, drug product containers, and closures.

- Use of approved components, drug product containers, and closures.
- Retesting of approved components, drug product containers, and closures.
- Rejected components, drug product containers, and closures.
- Drug product containers and closures.

- The component is assigned a control number that identifies both the component and the intended product.

- **Subpart F--Production and Process Controls**

- Written procedures; deviations. - Charge-in of components. - Calculation of yield. - Equipment identification. - Sampling and testing of in-process materials and drug products. - Time limitations on production. - Control of microbiological contamination. - Reprocessing.

- **Subpart G--Packaging and Labelling Control**

-Materials examination and usage criteria. - Labelling issuance. - Packaging and labeling operations. - Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. - Drug product inspection. - Expiration dating.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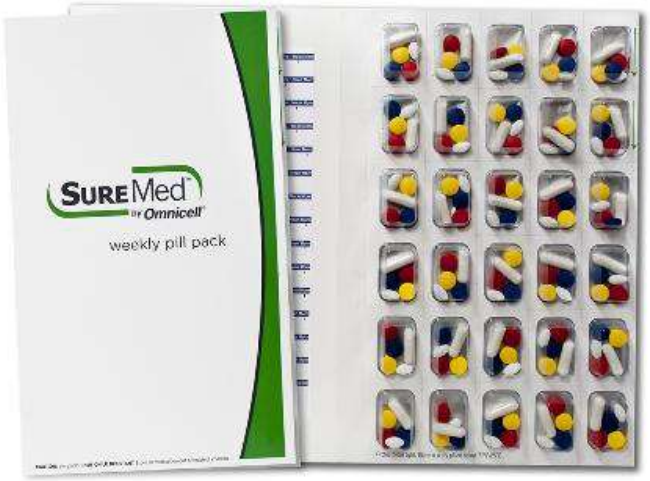
SUREMed
by Omnicell
weekly pill pack

- **Subpart H--Holding and Distribution**
- - Warehousing procedures. - Distribution procedures.

- **Subpart I--Laboratory Controls**
- - General requirements.
- - Testing and release for distribution
- - Stability testing.
- - Special testing requirements.
- - Reserve samples.
- - Laboratory animals.
- - Penicillin contamination.

Subpart J--Records and Reports

- General requirements.
- Equipment cleaning and use log.
- Component, drug product container, closure, and labeling records.
- Master production and control records.
- Batch production and control records.
- Production record review.
- Laboratory records.
- Distribution records.
- Complaint files.

Subpart K--Returned and Salvaged Drug Products

- Returned drug products. - Drug product salvaging.

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

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