UNIT-3 (LECTURE 2)

cGMP as per USFDA

cGMPs According to US FDA:

INTRODUCTION: Good Manufacturing Practice (GMP) ensures that quality is built into the organisation and processes involved in manufacture GMP covers all aspects of "manufacture" including collection, transportation, processing, storage, quality control and delivery of the finished product.

• It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product Protect the integrity and quality of manufactured product intended for human use.

PRINCIPLES OF cGMP:

• Design and construct the facilities and equipments properly
•Follow written procedures and Instructions
•Document work
•Validate work
• Monitor facilities and equipment
•Write step by step operating procedures and work on instructions
•Design, develop and demonstrate job competence
•Protect against contamination
•Control components and product related processes
•Conduct planned and periodic audits

LIST OF IMPORTANT DOCUMENTS IN cGMP:

•Policies
•SOPs
•Specifications
•MFR (Master Formula Record)
•Batch Package Records (BMR)
•Manuals
•Master plans/ files
•Validation protocols
•Forms and Formats
•Records

What are CGMP?

• c GMPs cover a broad range of methods, practices and principles that are implemented and documented during product development to ensure consistent manufacture of quality products
•the cGMP assures the identity, strength, quality, and purity of drug products is built into the design and manufacturing process at every step.
•" GMP is a dynamic concept and practice. Staying "current" is driven by technology, improved practices and regulatory issues.

USFDA REGULATIONS:

•The requirements for compliance to cGMP are lain down in the following code of Federal Regulation (21CFR).

•21 CFR Part 210 cGMP in manufacturing, processing, packing, or holding of the drugs

•21 CFR Part 211 cGMP for finished pharmaceutical.

•21 CFR Part 610 – Current Good Manufacture of Biological Products

•21 CFR Part 820 – Current Good Manufacturing Practices for Devices

Why are cGMPs so important?

•A consumer usually cannot detect that a drug product is safe. While cGMPs require testing, testing alone is not adequate to ensure quality.

•FDA will often use these reports to identify sites for which an inspection or investigation is needed.

Essential elements of cGMP are:

•Good Documentation Practices

•Training

•Facilities and Equipment Management

•Change Control Systems

•Operations Oversight and Management

CGMP for finished pharmaceuticals: part 211

•Subpart A - General Provision

•Subpart B - Organization & Personnel

•Subpart C - Building & Facilities

•Subpart D – Equipment

•Subpart E - Control of Components & Drug Product Containers & Closures

•Subpart F - Production & Process Control

•Subpart G - Packaging & Labeling Control

•Subpart H - Handling & Distribution

•Subpart I - Laboratory Control

•Subpart J - Records & Reports

•Subpart K - Returned & Salvaged Drugs

Subpart A-General Provisions

211.1 Scope:

(a) The minimum cGMP for preparation of drug products for administration to humans or animals.

(b) The requirements in this part shall not be enforced for OTC drug products and all their ingredients are ordinarily marketed and consumed as human foods.

211.3 Definitions:

The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in Parts 211

Subpart B-Organization and Personnel

211.22 Responsibilities of quality control unit:

(a) There shall be a QC 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 records.

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

211.25 Personnel qualifications:

(a) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it is represented to possess.

211.28 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.

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

211.34 Consultants:

It advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C-Buildings and Facilities

211.42 Design and construction features:

(a) Building shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

(b) adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, labeling , in-process materials, or drug products, and to prevent contamination.

211.44 Lighting:

Adequate lighting shall be provided in all areas.

211.46 Ventilation, air filtration, air heating and cooling:

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided

(c) Air filtration systems, including pre-filters and particulate matter air filters, shall be used.

211.48 Plumbing:

Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.

211.50 Sewage and refuse:

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

211.52 Washing and toilet facilities.
211.56 Sanitation.
211.58 Maintenance.
211.52-211.58 should be neat, clean and good

Subpart D-Equipment

211.63 Equipment design, size, and location:

Equipment shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

211.65 Equipment construction:

Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, so as to alter the safety, identity, strength, quality, or purity of the drug product

211.67 Equipment cleaning and maintenance:

•Equipment shall be cleaned, maintained, to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product.
•Inspection of equipment for cleanliness before use.
•Records shall be kept of maintenance, cleaning.

211.68 Automatic, mechanical, and electronic equipment:

(a) Equipments including computers, or related systems that will perform a function satisfactorily.
(b) They shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance.
(c)Written records of those calibration checks and inspections shall be maintained.

211.72 Filter:

(a) Fiber -releasing filters may not be used for injectable drug products unless it is not possible to manufacture such drug products without the use of such filters.
(b) If use of a fiber -releasing filter is necessary, an additional non- fiber -releasing filter of 0.22 micron maximum mean porosity shall subsequently be used to reduce the content of particles in the injectable drug product. Use of an asbestos-containing filter.

Subpart E-Control of Components and Drug Product Containers and Closures

211.80 General requirement: There shall be written procedures in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures.

211.82 Receipt and storage of untested components, drug product containers, and closures:

(a) They shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.
(b) They shall be stored under quarantine until they have been tested or examined, as appropriate, and released.

211.84 Testing and approval or rejection of components, drug product containers, and closures:

(a) The lot has been sampled, tested, as appropriate, and released for use by the quality control unit.
(b) Representative samples of each shipment of each lot shall be collected for testing or examination.

211.86 Use of approved components, drug product containers, and closures:
They shall be rotated so that the oldest approved stock is used first.
211.87 Retesting of approved components, drug product containers, and closures:
They shall be retested, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit.

Subpart F-Production and Process Controls
211.100 Written procedures; deviations:
There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.
211.101 Charge-in of components:
Components for drug product manufacturing shall be weighed, measured. If a component is removed from the original container to another, the new container shall be identified with the following information: (1) Component name (2) Receiving or control number; (3) Weight or measure in new container; (4) Batch for which component was dispensed, including its product name, strength, and lot number.
211.103 Calculation of yield:
Actual yields and % of theoretical yield shall be determined at manufacturing, processing, packaging, or holding of the drug product.
211.105 Equipment identification:
(a) Major equipment properly identified during production.
(b) Major equipment shall be identified by a distinctive identification number that shall be recorded in the batch production record to show the specific equipment used in the manufacture.
211.110 Sampling and testing of in-process materials and drug products:
(a) To assure batch uniformity and integrity of drug products,
(b) Written procedures shall be established that describe the in-process controls, and tests, to be conducted on appropriate samples of in-process materials of each batch.
211.111 Time limitations on production:
To assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product.
211.113 Control of microbiological contamination:
Written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures shall include validation
211.115 Reprocessing:
Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform to all established standards, specifications, and characteristics.

Subpart G-Packaging and Labeling Control
211.122 Materials examination and usage criteria:

There shall be written procedures describing in detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials ,materials that do not meet such specifications shall be rejected to prevent their use

211.125 Labeling issuance:

Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

211.130 Packaging and labeling operations:

(a) Prevention of mix-ups and cross-contamination by physical separation from operations on other drug products.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

211.132 Tamper-resistant packaging requirements for over-the-counter (OTC) human drug products:

211.134 Drug product inspection:

211.137 Expiration dating:

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use.

(b) It shall be related to any storage conditions stated on the labeling, as determined by stability studies

Subpart H-Holding and Distribution

211.142 Warehousing procedures:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

(c)Written procedures are necessary.

211.150 Distribution procedures:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first.

Subpart I-Laboratory Controls

211.160 General requirements:

(a) They shall include the establishment of, standards, sampling plans, and test procedures etc to confirm appropriate standards of identity, strength, quality, and purity.

(b)The calibration of instruments, apparatus, and recording devices at suitable intervals in accordance to written program

211.165 Testing and release for distribution:

(a) The sterility and/or Pyrogen testing are conducted on specific batches of short lived radiopharmaceuticals,

211.166 Stability testing:

(a) Stability testing shall be used in determining appropriate storage conditions and expiration dates.

(b)Accelerated studies, combined with basic stability information on the components, drug products.

211.167 Special testing requirements:

For each batch purporting to be sterile and/or Pyrogen -free, there shall be appropriate laboratory testing to determine conformance to such requirements.

211.173 Laboratory animals:

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained .They shall be identified, and adequate records shall be maintained showing the history of their use.

211.176 Penicillin contamination:

(a)If a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin.

(b) Such drug product shall not be marketed if detectable levels are found when tested according to procedures.

Subpart J-Records and Reports

211.182 Equipment cleaning and use log:

A written record of major equipment cleaning, maintenance and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed.

211.184 Component, drug product container, closure, and labeling records:

(a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier.

211.186 Master production and control records:

To assure uniformity from batch to batch and including each batch size thereof, shall be prepared, dated, and signed by one person and independently checked, dated, and signed by a second person.

211.188 Batch production and control records: Batch production and control records shall be prepared for each batch produced and shall include complete information relating to the production and control of each batch. (a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed; (b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished

211.192 Production record review:

All drug product, production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

211.194 Laboratory records:

It shall include complete data derived from all tests

211.196 Distribution records:

It shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

211.198 Complaint files:

All written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications

Subpart K-Returned and Salvaged Drug Products

211.204 Returned drug product:

(a) Products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return (b) if the condition of the drug product, its container, carton, or labeling , as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product

211.208 Drug product salvaging:

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, equipment failures shall not be salvaged and returned to the marketplace.