# SHAMBHUNATH INSTITUTE OF PHARMACY, JHALWA, ALLAHABAD

LECTURE NOTES
ON

## GOOD MANUFACTURING PRACTICES

## UNIT –III

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BY

**SAURAV GHOSHAL**
Asst. Prof.

# UNIT III

## 21-Code of Federal Regulation

The Code of Federal Regulations is a codification of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government. The Code is divided into 50 titles which represent broad areas subject to Federal regulation. Each title is divided into chapters which usually bear the name of the issuing agency. Each chapter is further subdivided into parts covering specific regulatory areas.

Each volume of the Code is revised at least once each calendar year and issued on a quarterly basis approximately as follows:

Title 1 through Title 16.....as of January 1
Title 17 through Title 27 .....as of April 1
Title 28 through Title 41 .....as of July 1
Title 42 through Title 50.....as of October 1

The appropriate revision date is printed on the cover of each volume.
LEGAL STATUS The contents of the Federal Register are required to be judicially noticed (44 U.S.C. 1507). The Code of Federal Regulations is prima facie evidence of the text of the original documents (44 U.S.C. 1510).

HOW TO USE THE CODE OF FEDERAL REGULATIONS

The Code of Federal Regulations is kept up to date by the individual issues of the Federal Register. These two publications must be used together to determine the latest version of any given rule.

To determine whether a Code volume has been amended since its revision date (in this case, April 1, 2012), consult the ‘‘List of CFR Sections Affected (LSA),’’ which is issued monthly, and the ‘‘Cumulative List of Parts Affected,’’ which appears in the Reader Aids section of the daily Federal Register.

These two lists will identify the Federal Register page number of the latest amendment of any given rule.

EFFECTIVE AND EXPIRATION DATES

Each volume of the Code contains amendments published in the Federal Register since the last revision of that volume of the Code. Source citations for the regulations are referred to by volume number and page number of the Federal Register and date of publication. Publication dates and effective dates are usually not the same and care must be exercised by the user in determining the actual effective date. In instances where the effective date is beyond the cutoff date for the Code a note has been inserted to reflect the future effective date. In those instances where a regulation published in the Federal Register states a date certain for expiration, an appropriate note will be inserted following the text.

**CURRENT GOOD MANUFACTURING PRACTICES GUIDELINES ACCORDING TO USFDA**

**Good manufacturing practice is generally abbreviated to GMP, in the USA the phrase used as CURRENT GOOD MANUFACTURING PRACTICES.**

**The code of FEDERAL REGULATION (CFR) is a compilation of all federal laws published in the FEDERAL REGISTER by executive departments and agencies of the federal government. Code is divided into 50 titles which represents broad areas of federal regulation each title is further divided into chapters. The chapters are than subdivided into parts covering specific regulatory areas. In the United states the production of the drug products is controlled under the federal food, drug and cosmetic act, which states that,"a drug product will be deemed to be adulterated unless the methods used in or the facilities or control used for its manufacture, processing, packaging or holding or administered in conformity with current GMP".**

**The US GMP regulations are divided into two parts: 210 and 211, title 21**

**Part 210 "current good manufacturing practice in manufacturing, processing, packing or holding of drugs- general," provides the framework for the regulation.**

**Part 211, "current good manufacturing practices for finished pharmaceuticals." States the actual requirements.**

**Part 210 - CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL**

210.1 Status of current good manufacturing practice regulations.
210.2 Applicability of current good manufacturing practice regulations.
210.3 Definitions.

210.1 Status of current good manufacturing practice regulations.
(a) The regulations set forth in this part and in Parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.
(b) The failure to comply with any regulation set forth in this part and in Parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such

drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

210.2 Applicability of current good manufacturing practice regulations.
(a) The regulations in this part and in Parts 211 through 226 of this chapter as they may pertain to a drug and in Parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.
(b) If a person engages in only some operations subject to the regulations in this part and in Parts 211 through 226 and Parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

210.3 Definitions.
(a) 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 through 226 of this chapter.

(b) The following definitions of terms apply to this part and to Parts 211 through 226 of this chapter. (1) Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).
(2) Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.
(3) Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.
(4) Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.
(5) Fiber means any particulate contaminant with a length at least three times greater than its width. (6) Non-fiber-releasing filter means any filter, which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos are deemed to be fiber-releasing filters.
(7) Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.
(8) Inactive ingredient means any component other than an ``active ingredient."

(9) In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.
(10) Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.
(11) Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.
(12) Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products.
(13) The term medicated feed means any Type B or Type C medicated feed as defined in 558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of Part 225 of this chapter.
(14) The term medicated premix means a Type A medicated article as defined in 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of Part 226 of this chapter.
(15) Quality control unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
(16) Strength means: (I) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or (ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).
(17) Theoretical yield means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.
(18) Actual yield means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.
(19) Percentage of theoretical yield means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.
(20) Acceptance criteria means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).
(21) Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

(22) Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

**PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS**

**Subpart A - General Provisions**

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**Subpart A-General Provisions**

The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

**Subpart B-Organization and Personnel**

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 or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

**Subpart C-Buildings and Facilities**

(a) 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.
(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mixups as follows: (1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures, and labeling before disposition; (3) Storage of released components, drug product containers, closures, and labeling;
(4) Storage of in-process materials;
(5) Manufacturing and processing operations;
(6) Packaging and labeling operations;
(7) Quarantine storage before release of drug products;
(8) Storage of drug products after release;
(9) Control and laboratory operations;
(10) Aseptic processing, which includes as appropriate:
(I) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
(ii) Temperature and humidity controls;
(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;
(iv) A system for monitoring environmental conditions;
(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions; (vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

**Subpart D-Equipment**

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

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

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.
(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination
(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.
(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

**Subpart F-Production and Process Controls**

(a) 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. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

**Subpart G-Packaging and Labeling Control**

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

(d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.

**Subpart H-Holding and Distribution**

211.142 Warehousing procedures. Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(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.

211.150 Distribution procedures. Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

**Subpart I-Laboratory Controls**

The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

**Subpart J-Records and Reports**

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

211.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit; (3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;
(6) A statement of theoretical weight or measure at appropriate phases of processing;
(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 211.192 is required;
(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;
(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.
211.196 Distribution records.

**Distribution records** 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. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

**Subpart K-Returned and Salvaged Drug Products**

211.204 Returned drug products.

Returned drug 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, or 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, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity.

A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

211.208 Drug product salvaging.

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is

(a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and
(b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

## DIFFERENCE BETWEEN GMP AND cGMP

All over the world, to help attain global standards, and to assist in giving people healthcare and pharmaceutical products that are of similar quality, GMP's have been accepted and followed by most of the countries of the world for the last 50 years. In fact, GMP's, called Goods Manufacturing Practices, have become guidelines that have helped maintain standards in these products across the world. Countries following GMP ensure quality of pharmaceutical products so that these products can be relied upon by people all over the world. Slowly and gradually, GMP's have become a pre requisite to export healthcare products between more than 100 countries of the world. It has become a trend to refer to GMP as cGMP. Here, c refers to current rules and regulations that serve the purpose of reminding manufacturers to strictly follow the guidelines and manufacturing procedures that are current and most up to date.

The use of c as a prefix to GMP is a an attempt by regulating authorities to make sure that countries, especially manufacturers who profess to follow the guidelines but still use 20-25 year old machinery and equipment to produce healthcare products are forced to change and adopt the latest and most advanced production procedures. This is a ploy that has certainly forced many manufacturers to give up on old practices and switch over to latest production processes. It has also helped in avoiding contamination, errors and mix ups while at the same time helping in production of highest quality healthcare and pharmaceutical products.

GMP guidelines are very broad in nature and cover all aspects of business such as personnel qualifications, cleanliness, book keeping, systems and procedures, equipment, and so on. In fact, GMP has helped in uplifting the standards of healthcare products and has strict regulations that accepting countries must adhere to. Companies that fail to comply with the provisions of GMP have to face serious consequences that include fines, jail, and recall of products and so on.

**In brief:**
**GMP vs CGMP**
• GMP refers to Goods Manufacturing Practices that are guidelines followed by over 100 countries
• GMP applies to pharmaceutical and healthcare products and help to maintain high standards in these products.
• cGMP is current goods manufacturing practices that need to be adhered to by participating countries.

• cGMP is to remind accepting countries that all guidelines must be followed with latest and current production processes.