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Good Manufacturing Practice (GMP) Guidelines (Eudralex-Volume 4)

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ABSTRACT

The basic rules in any good manufacturing practice (GMP) regulations postulate that the pharmaceutical manufacturer must maintain appropriate documentation and records. Documentation helps to build up a detailed interpretation of what a manufacturing function has done in the past and what it is doing now and, thus, it provides a base for planning what it is going to do in the future. Regulatory evaluators, during their inspections of manufacturing sites, often devote much time on examining a company's documents and records. Effective documentation boosts the visibility of the quality assurance system.

KEY WORDS: *GMP, 21 CFR, Part 210 and 211, Documentation, Regulations Agencies*

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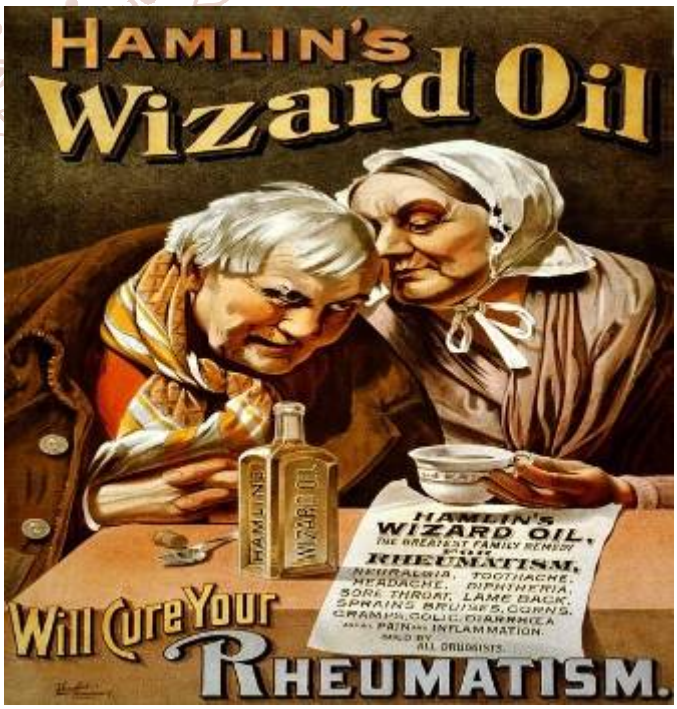
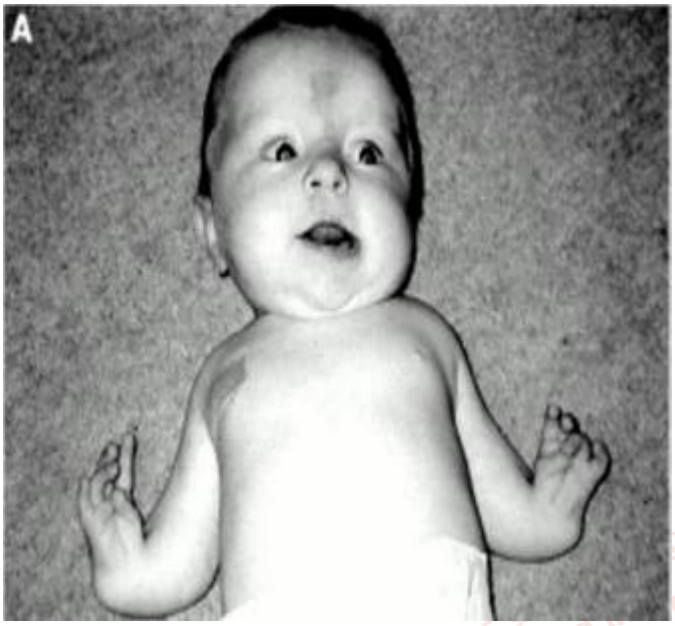
HISTORY OF GMP

- US patented medicine, first produced in 1861 in Chicago by former magician John Austen Hamlin and his brother Lysander Butler Hamlin
- Primarily sold and used as liniment for rheumatic pain and sore muscles
- Was also advertised as a treatment for cancer, pneumonia, diphtheria, earache, toothache headache and hydrophobia.
- Made of 50% - 70% alcohol containing camphor, ammonia, chloroform, sassafras, cloves and turpentine and was said to be usable both internally and topically In 1916, Lysander's son Lawrence B. Hamlin, was fined $200 under the 1906 Pure Food and Drug Act for misbranding it as a 'cancer drug'



WHAT HISTORY TEACHES US…… PHARMACEUTICAL DISASTERS

Thalidomide Tragedy: Thousands of children born with birth defects due to adverse drug reactions of morning sickness pilltaken by mothers



Contamination: Sulfathiaziole tablets contaminated with phenobarbital- 300 people died/injured….

GOOD MANUFACTURING PRACTICES (GMP)

DEFINITION:

GMP is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by the marketing authorization.

Good Manufacturing Practices (GMPs) are regulations that describe the methods, equipment, facilities, and controls required for producing:

- Human and veterinary products
- Medical devices
- Processed food

Usually see "cGMP" – where c = current, to emphasize that the expectations are dynamic. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

These regulations, which have the force of law, require that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood take protective steps to ensure that their products are safe, pure, and effective.

Require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors.

Protects the consumer from purchasing a product, which is not effective or even dangerous. GMP regulations address issues including record keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling.

In short GMP makes the difference between nearly right and exactly right.

WHY GMP?

- Final testing of the product cannot ensure the Quality efficiency and safety.
- Final testing may always not detect contamination, error, etc.
- Conformance to the predetermined specification.
- To minimize contamination eg:- microbial contamination.
- To eliminate error.
- To produce product of consistent quality.
- Government requirement.
- Ensure quality product.
- Reduce rejects, recalls.
- Satisfied customers.
- Company image and reputation.

CODE OF FEDERAL REGULATIONS (CFR):

- It is the Portion of FDA.
- The collection of final regulations published in the federal register (daily published records of proposed rules, final rules, meeting notices, etc.
- Divided into 50 titles.
- Current regulations of GMP appear in part **210 (title 21) of code of federal regulations** published by **USFDA.**

REGULATIONS AGENCIES

- CDSCO – India Central Drug Standards Control Organization
- FDA – U.S. Food and Drug Administration
- EMA – European Medicines Agency
- ANVISA – Brazil (Agência Nacional de Vigilância Sanitária)
- MHRA – Medicines & Healthcare Regulatory Agency
- SFDA – Saudi Food and Drug Authourity
- WHO – World Health Organization

GUIDANCE DOCUMENTS

- Pharmacopoeia (IP, US, EU, JP...)
- CFR - US Code of Federal Regulations
- ISPE Baseline guides
- GMPs (Brazil, China, India...)

21 CFR, PART 210 AND 211 CURRENT GOOD MANUFACTURING PRACTICE AN QUICKVIEW OF THE FDA REGULATIONS

21 CFR Part 11

Introduction

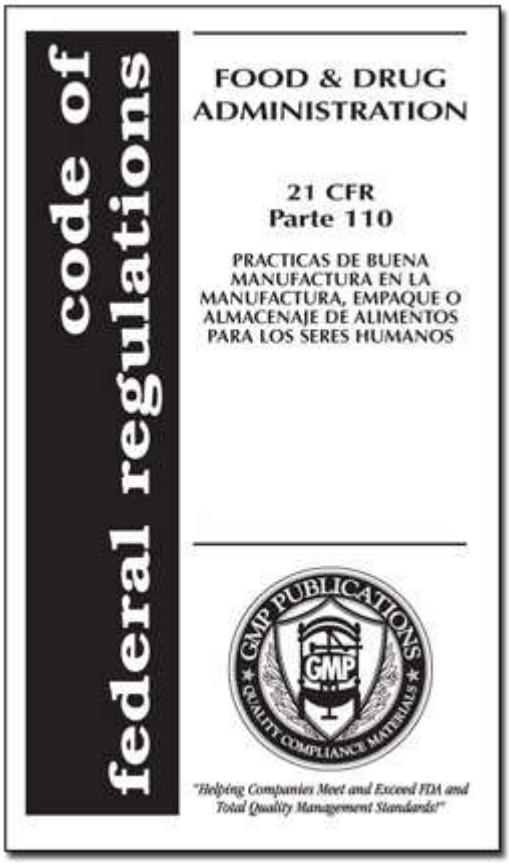
CFR – Code of Federal Regulations (Administrative Law) – 50 titles

The CFR is divided into 50 titles that represent broad subject areas:

- Title 1: General Provisions
- Title 2: Grants and Agreements
- Title 3: The President
- Title 4: Accounts
- Title 5: Administrative Personnel
- Title 6: Domestic Security
- Title 7: Agriculture
- Title 8: Aliens and Nationality
- Title 9: Animals and Animal Products
- Title 10: Energy
- Title 11: Federal Elections
- Title 12: Banks and Banking
- Title 13: Business Credit and Assistance
- Title 14: Aeronautics and Space (also known as the Federal Avia
- Title 15: Commerce and Foreign Trade
- Title 16: Commercial Practices
- Title 17: Commodity and Securities Exchanges
- Title 18: Conservation of Power and Water Resources
- Title 19: Customs Duties
- Title 20: Employees' Benefits
- Title 21: Food and Drugs
- Title 22: Foreign Relations
- Title 23: Highways
- Title 24: Housing and Urban Development

Title 21 – Food and Drugs

210 CGMP in Manufacturing, Processing, Packaging or holding drugs – General
211 CGMP of Finished Pharmaceuticals



Part 210 General

Status of the regulations

- Regulations set forth are "minimum" requirements!!!!
- Covers manufacturing, facilities and controls for
  - Manufacturing, processing, packaging or holding of a drug product
- Failure to comply will render the drug to be adulterated
  - The person who is responsible for the failure to comply shall be subject to regulatory action.

Applicability:- Applies to drug products for human use

Definitions

- **Batch:-** A specific quantity of drug/material intended to have uniform character and quality produced under a single manufacturing order form during the same cycle of manufacture.
- **Component:-** Any ingredient intended for use INCLUDING those that may not appear in such drug product
- **Drug Product:-** Finished dosage form
- **Fiber:-** Any particulate with a length at least 3 times to its width
- **Active ingredient:**- Any component intended to furnish pharmacological activity
- **Drug:**- Drug is defined by the Act as any compound that has effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or function of the body of man or animals
- **In-process material:**- Any material fabricated, compounded, blended or derived for use in the drug product**.**
- **Manufacture, processing, packing or holding includes:-** Packaging and labeling, testing and quality control of drug products
- **Quality Control:**- Any person or unit designated by the firm to be responsible for duties relating to QC
- **Representative Sample:**- Samples drawn on rational criteria intended to accurately portray the material being sampled

21 CFR Part 211

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

Subpart A General Provisions

Scope

- Minimum requirements
- Applies to drugs for human use

Definitions

- Those set forth in 210.3 are applicable

Subpart B Organization and Personnel

211.22 Responsibilities of QC

The QC unit shall have adequate laboratory facilities

- They shall have the responsibility for approving/rejecting all procedures or specifications impacting the quality of the drug product
- Responsibilities shall be in writing and shall be followed.

211.25 Personnel Qualifications

- Everyone shall have the education, training and experience to do their jobs.
- Everyone who supervises those people shall have the education, training and experience to assign functions to provide assurance for drug quality.
- There shall be an adequate number of qualified personnel.

211.28 Personnel Responsibilities

- Wear clean clothing and protective apparel
- Practice good sanitation and health habits
- Limited access areas
- If you are sick – do you belong in the area

211.34 Consultants

- Shall have sufficient education, training and experience to advise on the subject matter.
- Records maintained stating the name, address and qualifications of consultants.

SUBPART C – BUILDINGS AND FACILITIES

211.42 Design & Construction

- Any building shall be maintained to facilitate cleaning, maintenance and proper operations
- Adequate space
- Operations performed in defined areas
- Receipt, storage, holding, etc.
- All operations
- Penicillin operations in separate area

211.44 Lighting

- Adequate lighting provided

211.46 Ventilation

- Adequate ventilation
- Adequate equipment for control of environment (micro, dust, air-pressure)
- Air filtration provided

211.48 Plumbing

- Potable water supplied under continuous positive pressure
- System free of defects
- Potable water meeting EPA requirements (40 CFR, Part 141)
- Drains of adequate size
- Back-flow prevention

211.50 Sewage and Refuse

- Dispose of trash, sewage and other refuse in a safe and sanitary manner

211.52 Washing and toilet facilities

- Adequate washing facilities shall be provided
- Hot and cold potable water
- Soap and detergent
- Air dryers or single-service towels
- Easy access to working areas

211.56 Sanitization

- Facilities shall be maintained in a clean and sanitary condition
- Free of rodents, birds, insects
- There shall be written procedures on cleaning schedules, methods, equipment and materials
- Shall be written procedures for rodent ides, insecticides, fungicides
- Facilities shall be maintained in a good state of repair

SUBPART D – EQUIPMENT

211.63 Equipment design, size and location

- Equipment shall be of appropriate design, adequate size and suitably located to facilitate operations, cleaning and maintenance

211.65 Equipment construction

- Equipment material of construction not be reactive with product.
- Lubricants/coolants shall not come into contact with product to alter the quality of the product

Equipment cleaning and maintenance

- Equipment and utensils shall be cleaned, maintained and sanitized to prevent malfunctions and contamination
- Written procedures shall be established for cleaning and maintenance of equipment, utensils.
- Records shall be kept of maintenance, cleaning, sanitizing and inspection.

Automatic, Mechanical & Electronic Equipment

- Automatic, mechanical and electronic equipment, computers, etc. used in the manufacturing area shall be routinely calibrated, checked and inspected as per written procedure with retained records of calibrations, inspections, etc.
- Computers systems documentation and validation documentation shall be maintained.
- Computer systems electronic records must be controlled including records retention, backup, and security.

211.72 Filters

- Shall not release fibers into drug products
- If fiber releasing filters are necessary
- Additional filtering using 0.22 micron max porosity
- 0.45 if manufacturing conditions so dictate
- Use of asbestos-containing filter is allowed only after proving to FDA safety or effectiveness is not compromised

SUBPART E – CONTROL OF COMPONENTS AND DRUG PRODUCT CONTAINERS AND CLOSURE

211.80 General Requirements

- Written procedures shall be made and followed for receipt, sampling, approval, rejection.
- Handle and store in a manner to prevent contamination
- Bagged or boxed items shall be stored off of the floor and be adequately space for cleaning and inspection
- Each Lot/container shall be identified with code for each lot received and status (quarantined, approved, rejected).

211.82 Receipt and Storage

- Shall be examined visually for appropriate labeling as to contents, container damage/seals broken, contamination, etc upon receipt.
- Materials shall be quarantined until tested and released.

211.84 Testing and Approval/Rejection

- Materials shall be withheld from use until tested and released for use by Quality Control.
- From each lot shall be sampled upon appropriate statistical criteria.
- Samples collection
- Clean the container if necessary
- Collect the samples in designated area to prevent contamination
- Samples shall be identified with lot#, date, and done by, etc.
- Containers must show samples were taken

- Samples shall be tested for at least one identification test.
- COA of manufacturer shall be acceptable provided by at least one specific identification test by establishing vendor evaluation.
- Any lot that does not meet the specifications shall be rejected.

Use of Approved components

- Materials shall be used/issued in FIFO.
- Deviation of FIFO shall be permitted, if temporary and appropriate.

Retesting

- Materials shall be retested after storing a long time might be have adverse affect on quality due to exposure to air, heat etc.

211.89 Rejected materials

- Rejected materials shall be stored under designated area to prevent the use for manufacturing.

211.94 Drug product containers and closures

- Provide protection from external factors that could contaminate or deteriorate drug
- Shall not be reactive, additive or absorptive as to adversely effect product
- Clean and suitable for use
- Specification and test methods shall be written and followed.

SUBPART F – PRODUCTION & PROCESS CONTROLS

Written procedures; deviations

- Written procedures shall be established and followed for Production (BMR) and process controls (in-process, Intermediate spec.)
- Process control functions shall be recorded at the time of performance.
- Any deviation from the established procedure shall be recorded and justified.

Charge-in of components

- Each batch formulation should attempt to make 100% of specified active ingredient
- Components for manufacturing shall be weighed, measured, or subdivided as appropriate and should be verified by second person.
- QC released/approved
- Containers are identified & Weight/measurement is correct per batch record
- When a component is transferred to a non-original container, it shall indicate – Name, item code,– Receiving/control number,– Weight/measurement in new container, – Batch for which component was issued including name, strength and lot number, Each component added to the batch shall be verified by the second person

211.103 Calculation of yield

- Actual yields and percentages of theoretical yield shall be determined at the conclusion of each stage of manufacturing, processing, packaging, or holding of the drug product.
- Such calculations shall either be performed by one person and independently verified by a second person.

211.105 Equipment identification

- Storage containers, processing lines, and major equipment used during the production shall be properly identified.
- Major equipment shall be identified by number or code that shall be recorded in the batch production record to show the specific equipment used.

211.110 Sampling and testing of in-process materials

- In-process specifications shall be consistent with final specifications
- In-process materials tested for quality, strength & purity & be accepted or rejected by QC
- Rejected material shall be quarantined in order to prevent use in Manufacturing

211.111 Time limitations on production

- When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the product.
- Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

211.113 Control of microbiological contamination

- Written procedures shall be established and followed to prevent objectionable microorganisms in drug products of non-sterile.
- Written procedures shall be established and followed to prevent microbiological contamination into sterile drug products, Such procedures shall include validation.

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- Such procedures shall include validation.

211.125 Labeling issuance

- Strict control shall be exercised over labeling issued for use
- Compare issued materials to master
- Reconciliation of labels should be maintain
- All excess labeling bearing lot or control numbers shall be destroyed
- Written procedures shall be established and followed for the issuance of labeling
- Returned materials shall be stored separately to prevent mix-ups

211.130 Packaging and labeling operations

- Written procedures shall be established and followed for Packaging and Labeling operations, procedure shall cover the following
- Prevention of mix-ups & contamination
- Identification and handling of set aside filled but unlabeled product.
- Identification of the drug product with a lot or control
- Examination for suitability and correctness before packaging operations
- Inspection of packaging & labeling facilities to ensure the previous products are removed and cleaned
- 211.134 Drug product inspection
- Packaged and labeled product should be final inspected to assure correct labeling
- A sampling of units shall be collected and inspected for correctlabeling
- Results of inspection shall be recorded in batch record

211.137 Expiration dating

- Expiration date should be determined by stability testing
- Label shall be reflect the storage condition determined by stability testing
- Expiration date shall be bear on label for the products to be reconstituted and un-reconstituted
- Expiration dates must be reflect on labeling

SUBPART H –HOLDING AND DISTRIBUTION

211.142 Warehousing procedures

- Quarantine of drug products before release by the quality control unit
- Storage of drug products under appropriate conditions which may not affect the quality/strength

211.150 Distribution procedures

- Oldest products are distributed first.
- Deviation is permitted if it is temporary and appropriate
- Distribution records should be maintain to facilitate recall if required/necessary

SUBPART I –LABORATORY CONTROLS

211.160 General requirements

- Written procedure shall be established and followed for specification, test procedures, sampling and scientifically sound.
- Any deviation from established shall be recorded, justified
- Instruments calibrations should be performed as per procedures and schedules
- Instruments which are failed don not use.

211.165 Testing and release for distribution

- Every batch should meet the specification prior to release
- Sampling and testing plans should be described in written procedure
- Validated method should be employed for testing
- Any batch, not met the specification shall be rejected

211.166 Stability testing

- Stability studies should be performed.
- Stability sample should be simulated to the market
- Written procedure should be available with the following details
- Sample details (Quantity, batch # etc.)
- Testing interval
- Stability conditions
- Stability specifications

211.170 Reserve sample

- Representative of each batch sample shall be retained.

- Sample quantity consists of two complete analysis
- Sample should be simulated to the market
- Sample should be retained up to 1 year after expiration.
- Sample should be examined visually once in a year for any deterioration and to recorded

211.173 Laboratory animals

- Penicillin controlled in separate facility
- If, exposed to penicillin, the product shall be tested for the presence of penicillin. Such drug product shall not be marketed until they complies as per FDA requirements.

SUBPART J –RECORDS AND REPORTS

- Records shall be retained for at least 1 year after the expiration date
- All records or copies of such records shall be readily available for review/inspection
- Product quality review should be performed once in a year

211.182 Equipment cleaning and use log

211.180 General Requirements

- Equipment usage records should be maintain.

211.184 Container, closure, and labeling records

- Records shall be maintain, including
- Supplier name and lot number
- Date of receipt
- Approved/Rejected
- Label shall be compared with master

211.186 Master production and control records

- Master production and control records shall be maintain
- Made by one person and checked by another (prepared, dated, signed –full signature)
- Complete list of components
- Accurate statement of weights, reasonable variations
- Theoretical reconciliation

211.188 Batch production and control records

- Batch production and control records shall be maintain, includes
- Operation dates & Equipments used
- List of materials and quantities
- In-process results
- Actual yield & Theoretical yield
- Deviations
- Done by & Checked by sign

211.192 Production record review

- Batch records including packaging and labeling, shall be reviewed and approved prior to release.
- If any batch failed to meet the specifications shall be investigated and recorded.
- The investigation shall extend to other batches … that may have been associated with the specific failure or discrepancy
- A written record of the investigation shall be made and shall include the conclusions and follow-up.

211.194 Laboratory records

Lab records include complete data from all tests: Description of sample received & Statement of each method

- Complete record of all data –graphs, charts
- Initials of person doing test and dates
- Initials of person checking and dates
- Calibration data maintained
- Stability records maintained

211.196 Distribution records

- Distribution records shall be maintained
- Who, where, what, quantity

211.198 Compliant files

- Complaint files shall be maintained
- Investigations performed
- Include name of product, lot number, name of complainant, nature of complaint, reply

SUBPART K –RETURNED AND SALVAGED DRUG PRODUCTS

211.204 Returned drug products

- Returned products identified and held
- If conditions of return or storage are in doubt, investigation is warranted
- Procedures shall be in writing

211.208 Drug product salvaging

- Product subjected to improper storage conditions due to disaster or accident shall not be salvaged
- Unless,
- Tests can show everything is OK
- Evaluation of conditions indicates product was not exposed to such harsh conditions

Eudralex-Volume 4 of **"The rules governing medicinal products in the European Union"**contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use

PART I- BASIC REQUIREMENTS FOR MEDICINAL PRODUCTS

- Chapter1- Pharmaceutical Quality System
- Chapter2- Personnel
- Chapter3- Premise and Equipment

Chapter4-Documentation
Chapter5- Production
Chapter6- Quality Control
Chapter7- Outsourced activities

Chapter8-Complaints and Product Recall
Chapter9- Self Inspection

PART II-BASIC REQUIREMENTS FOR ACTIVE SUBSTANCES USED AS STARTING MATERIALS

PART III- GMP RELATED DOCUMENTS

Site Master File

Q9 Quality Risk Management

Q10 Note for Guidance on Pharmaceutical Quality System

ORGANIZATION AND PERSONNEL

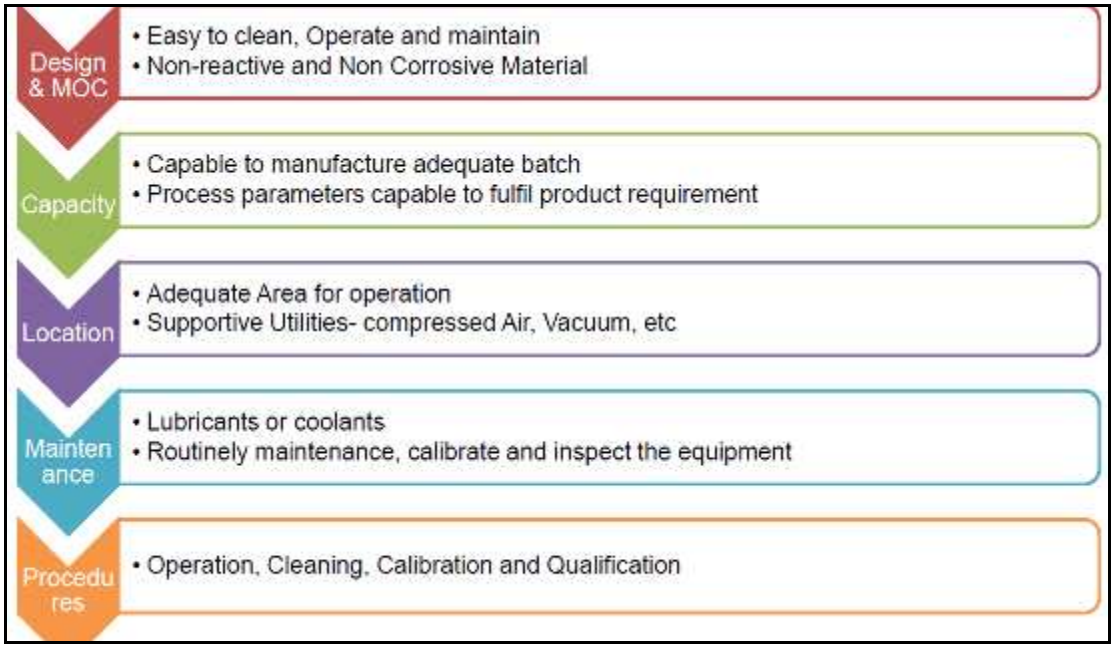
- Sanitation and Hygiene-Personnel Hygiene

HEALTH

- Health Examination for personnel in manufacturing and laboratory areas shall be done at the time of recruitment.
- Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or drug products until the condition is no longer judged to be a risk.

BUILDING & FACILITY

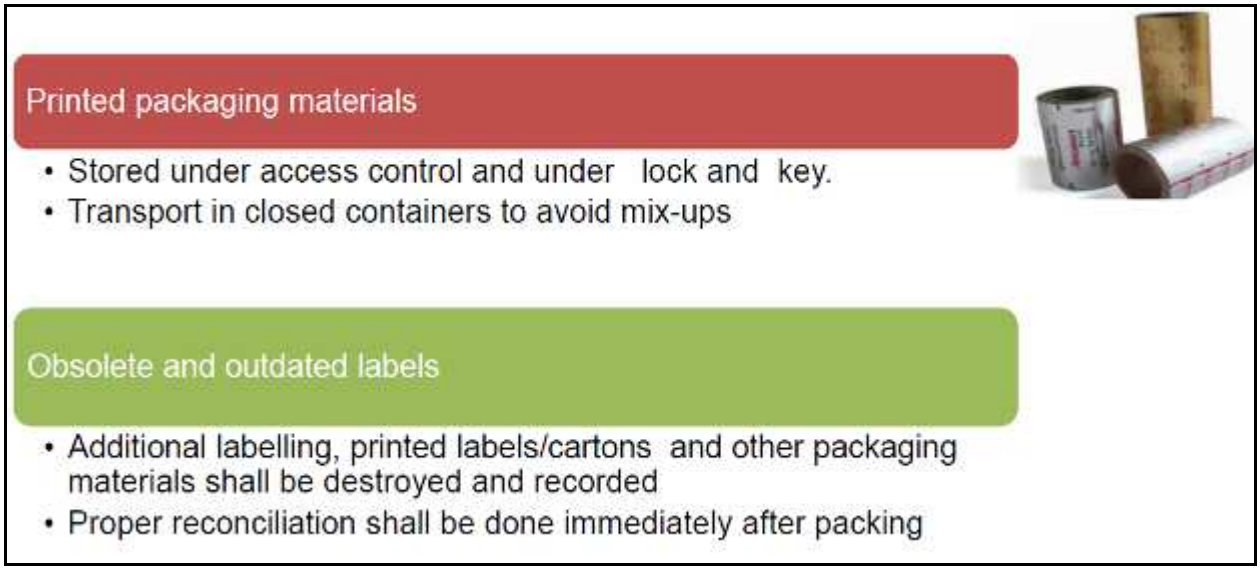
EQUIPMENT



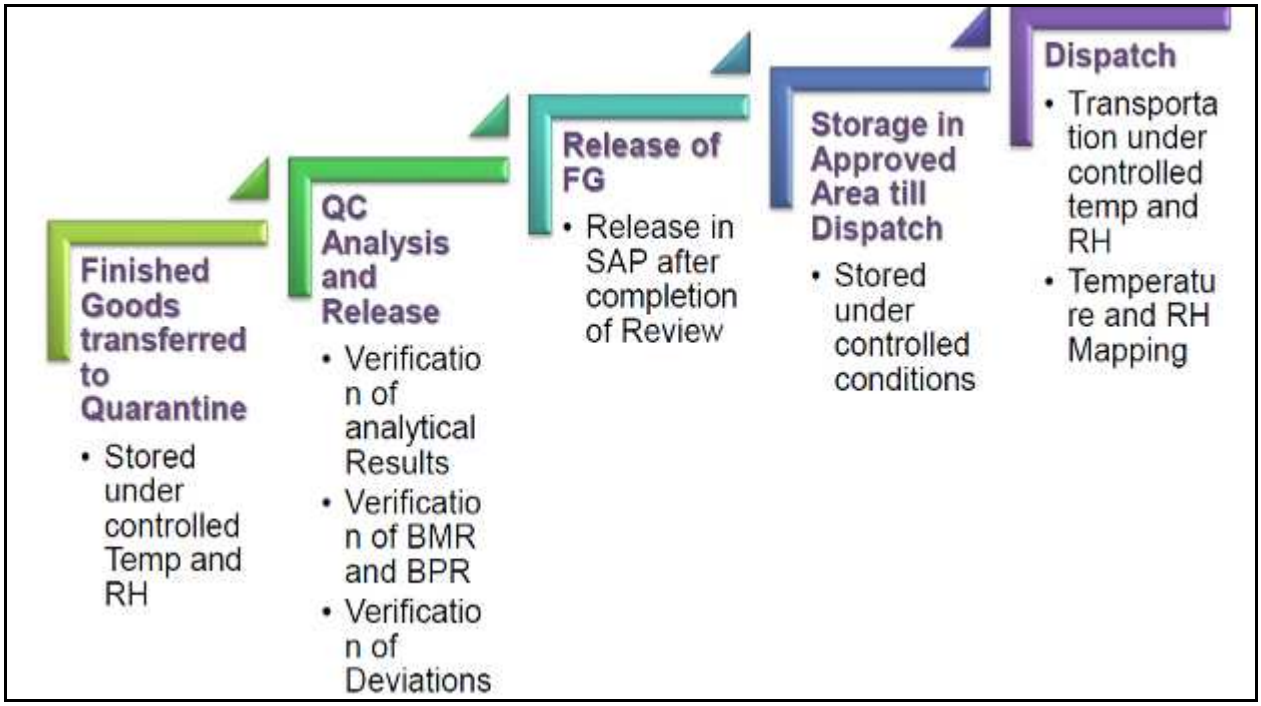
MATERIALS

MATERIALS STORAGE

PACKAGING AND LABELLING CONTROL



HOLDING AND DISTRIBUTION



COMMON PROBLEMS IN GMP EXECUTION:

1. Organization:
- Lack of commitment
- Lack of resources for execution

2. Layout & Construction:
- No quarantine area
- Insufficient environmental monitoring
- Cracked floor

3. Equipment:
- No calibration
- No performance check of balance before use
- Rusty
- Parts not kept improperly

4. Laboratory Testing:
- Poor reference standard keeping
- Poor data recording
- Reagent with no label

5. Documentation & Recording:
- No signature; no countercheck
- Improper correction made
- No written procedure
- Incomplete complaint record
- No up-to-date training record
- No document review

6. Labelling:
- Status not defined clearly
- Poor labelling control
- Release label not kept securely
- Inadequate reconciliation of batch label
- Defective equipment with no label

7. Validation:
- Insufficient validation
- Insufficient raw data
- No validation programme

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