

CHAPTER 1

GMP Regulations for Pharmaceutical Industry

Introduction

A GMP is called as Good Manufacturing Practices and cGMP is called as current Good Manufacturing Practice. GMP is a system which ensuring that products are consistently produced and controlled according to quality standards and regulations, which protect the patient. GMP covers all aspects of production from the starting materials, premises and equipment to the training and personal hygiene of staff. Compliance with GMP is a necessary condition for the Marketing Authorization to sell the product. Standards are not legal rules they are guidelines, but nevertheless when linked to enforcement regimes and sanctions can be very powerful. cGMP always focus on Quality management, Quality assurance, Evaluation analysis, Quality risk management tools, Correction, Preventive action, Risk management and Continuous improvement.

1.1 Basic Requirements of GMP

- (a) Manufacturing processes are clearly defined and controlled to ensure consistency and compliance with approved specifications.
- (b) Critical steps of manufacturing processes and significant changes to the process are validated.
- (c) Key elements for GMP including the following:
 - Qualified and trained personnel,
 - Adequate premises and space,
 - Suitable equipment and services,
 - Correct materials, containers and labels,

2 **GMP in Pharmaceutical Industry: Global cGMP & Regulatory Expectation**

- Approved procedures and instructions,
 - Suitable storage and transport.
- (d) Instructions and procedures are written in clear and unambiguous language.
- (e) Operators are trained to carry out and document procedures.
- (f) Records are made during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.
- (g) Records of fabrication, packaging, labelling, testing, distribution, importation, and wholesaling that enable the complete history of a lot to be traced are retained in a comprehensible and accessible form.
- (h) Control of storage, handling, and transportation of the drugs minimizes any risk to their quality.
- (i) A system is available for recalling of drugs from sale.
- (j) Complaints about drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

1.2 **Organization Pillars in cGMP**

- (a) **Management responsibilities:** Management play a key role in the design and implementation of quality system n cGMP. Leadership, structure organization, established policy, approved procedure, plan and review of system are root of the robust quality system.
- (b) **Resources:** Senior management, or a designee is responsible for adequate resources such personnel, facilities, equipment, training, out sourcing activities, for robust quality system which involves in problem-solving and communicative organizational culture.
- (c) **Manufacturing operations:** The product and process characteristics from design, development and commercial with input material, resource involved: facility, equipment and personnel, environment monitoring, monitoring of process and quality control testing.
- (d) **Evaluation activities:** Continually monitoring trends and improving systems.

1.3 Six Quality System in GMP

Quality system is a centre hub which is connected to five other manufacturing subsystem such as Production System, Facilities and Equipment System, Laboratory Controls System, Materials System, Packaging and Labelling System. They are interlinked to each other to system is state of control.

A. Pharmaceutical Quality Management System

Quality management system a set of interaction elements designed to maintain the regulatory guideline, regulation, policies, resources, approved procedure, quality objective and risk assessment. It helps to develop an effective monitoring and continual improvement in product quality. Following are the aspects of:

- Defines the quality of product characteristics which have established identity, strength, purity, and potency.
- Product knowledge and process understanding from drug development to the commercial manufacturing.
- Quality Risk Management to mitigate the risk of changing a process or specification, and determine the extent of discrepancy investigations and corrective actions.
- CAPA (Corrective and Preventive Action): Remedial corrections of an identified problem, Root cause analysis with corrective action to help understand the cause of the deviation and potentially prevent recurrence of a similar problem and preventive action to avert recurrence of a similar potential problem.
- Focuses on managing change to prevent unintended consequences.
- Defines responsibility between quality control (QC) and quality assurance (QA) functions.

B. Production Management System

Production operations must be carried out accordance with the relevant manufacturing and marketing authorizations by competent people. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution must done as approved procedure. Real time documentation must be performed during each and every operation. Yield and

reconciliation shall be carried out to check for acceptable limit. Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination. Risk assessment shall be carried out based on technical and organizational measures

a. Technical Measures

- Dedicated manufacturing facility (premises and equipment);
- Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;
- Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning;
- Use of “closed systems” for processing and material/product transfer between equipment;
- Use of physical barrier systems, including isolators, as containment measures;
- Controlled removal of dust close to source of the contaminant e.g. through localised extraction;
- Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;
- Use of single use disposable technologies;
- Use of equipment designed for ease of cleaning;
- Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;
- Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

- Use of automatic clean in place systems of validated effectiveness;
- For common general wash areas, separation of equipment washing, drying and storage areas.

b. Organisational Measures

- Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;
- Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;
- Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;
- Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;
- Specific measures for waste handling, contaminated rinsing water and soiled gowning;
- Recording of spills, accidental events or deviations from procedures;
- Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;
- Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

- Use of common general wash areas on a campaign basis;
- Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.
- Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set.

C. Facilities and Equipment Management System

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products. Facility and equipment must identify with specific number, qualify and validate at its operating range. Periodically check of facility and equipment must be carried out to check state of control. Equipment must adequately design and easily cleaned with its approved cleaning procedure. Calibration and Planned preventive maintenance program must be design. Pipelines and utilities must be mark with coding and direction. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

D. Laboratory Controls Management System

Quality Control is concerned with sampling, specifications and testing as well as the organization,

Documentation and release procedures which ensure that the necessary and relevant tests are carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

E. Materials Management System

Ware house areas must be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items. Ware house must be maintained clean free from rodent and environment control. It should separate loading and unloading bay protected from adverse whether, separated sampling and dispensing area.

- Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure areas.
- Printed packaging materials shall be stored in safe, separate and secure area.
- Separate dispensing areas for β (Beta) lactum, Sex hormones and Cytotoxic substances or any such special categories of product shall be provided with proper supply of filtered air and suitable measures for dust control to avoid contamination. Such areas shall be under differential pressure.
- Sampling and dispensing of sterile materials shall be conducted under aseptic conditions conforming to Grade A, which can also be performed in a dedicated area within the manufacturing facility.
- Regular checks shall be made to ensure adequate steps are taken against spillage, breakage and leakage of containers.
- FIFO (Frist in first out) and FEFO (Frist expiry first out) inventory management.
- Inventory management

F. Packaging and Labelling Management System

Packaging and labeling concerned about label affixed to the product which gives identity to the product. The label manufacturer is responsible for making sure that the print is legible and will remain that way throughout the product's life span. Every label printed should be inspected thoroughly to

ensure the information is consistent and accurate. The products should be separated to prevent any mix-ups or switches. Product separation can be physical or spatial, or can be completed by performing press runs at different times to avoid confusion. Proper storage control is necessary for preventing any mix-ups or switches when dealing with labels printed for use in the pharmaceutical industry

Before packaging operations are begun,

- Ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used.
- Correct product name batch number on each packing station line.
- The line-clearance must be performed according to an appropriate check-list. All products and packaging materials quantity to be used should be checked for code number, retest date and expiry date.
- Re-checked at regular intervals.
- Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
- Electronic code readers, label counters or similar devices are operating correctly.
- Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- On-line control of the product during packaging should include at least checking the following:
 - a. General appearance of the packages;
 - b. Whether the packages are complete;
 - c. Whether the correct products and packaging materials are used;
 - d. Whether any over-printing is correct;
 - e. Correct functioning of line monitors.

- Samples taken away from the packaging line should not be returned.

Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock.

1.4 Quality Culture and Pharmaceutical Industry

Culture means core value, guide, principles, behaviors and Attitudes. Quality culture in an organization is drives through the policies, practices, and processes used to accomplish an organization's work. Quality culture can build by understanding organization environment.

Who we are? Where we are? Where we want to reach? How we can do?

The culture of an organization is the embodiment of the core values, guiding principles, behaviors, and attitudes that collectively contribute to its daily operations. Culture drives the policies, practices, and processes used to accomplish an organization's work.

Quality culture will be developed by transparent and open by communicating the information at all level. An organization shall create a work environment transparent and open, one in which personnel are encouraged to freely communicate failures and mistakes, including potential data reliability issues, so that corrective and preventative actions can be taken.

An organization can foster quality culture by:

- Trust among each and every employee
- Code of Ethics and Code of Conduct: Not on paper base. By understanding and awareness for personnel.
- An organization should demonstrate the behaviors they expect to see from top to low management.
- Ensure accountability for actions and decisions.
- Stay continuously and actively involved.
- Set realistic expectations, consider the limitations that place pressures on employees.
- Allocate resources to meet expectations.

10 GMP in Pharmaceutical Industry: Global cGMP & Regulatory Expectation

- Implement fair and just consequences and rewards and
- Be aware of regulatory trends to apply lessons learned to your organization.
- Investigation programs and problem solving and Review practice.
- Training program and decision making and Regular management review of quality metrics.
- Resource allocation, Team spirit, Role models.
- Continuous improvements and motivation.
- It is the collection of values, beliefs, thinking, and behaviors demonstrated consistently by management, team leaders, quality personnel and all personnel that contribute to creating a quality culture in an organization.