



LATEST TREND IN DRUGS REGULATORY GUIDANCE ON 'GOOD MANUFACTURING PRACTICES'

Nirmal Kumar¹, M.S.

Prof. Ajeya Jha¹, M.Pharm, Ph.D.

¹ Sikkim Manipal Institute of Technology, Majitar, Sikkim, -737132, India
e- mail: nirmal.quality@gmail.com

ABSTRACT : *The Good Manufacturing Practices (GMP) is the synonym of Quality Management System in pharmaceutical industry across the world. The manufacturer should assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. GMP are aimed primarily at controlling the risks inherent in any pharmaceutical production.*

Such quality risks are essentially of two types: (a) Cross-contamination (expected or unexpected contaminants) and (b) Mix-ups (confusion due to mislabeling) caused by, for example, false labels being put on in-process containers.

Keywords – *Quality Management System, CGMP, ICH, USFDA, WHO*

I. INTRODUCTION

The Good manufacturing practice (GMP) is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP is a system for corroborating that products are consistently produced and controlled according to approved quality standards. It is designed to minimize the quality risks involved in any pharmaceutical production that cannot be eliminated through inspection or testing the final products.

The GMP covers all aspects of production from the starting materials, premises, instrument, and equipment to the training and personal hygiene of staff. Detailed, documented and written procedures are essential for each process that could affect the quality of the finished product. There shall be systems to provide documented proof that correct procedures are consistently followed at each critical step in the manufacturing process - every time a product is made.

The GMP is also sometimes referred to as "cGMP". The "c" stands for "current," reminding manufacturers that they must employ technologies and systems which are up-to-date in order to comply with the regulation. Updated systems and equipment used to prevent contamination, mix-ups, defects and errors, which may have been "top-of-the-line" 15-20 years ago, may be less than adequate by current standards.



The regulatory bodies want quality assurance approach throughout the manufacturing process. As per World Health Organization (WHO) the “Quality Assurance” is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including design and development.

The leading international regulatory agencies have collaborated to produce one harmonised guidance for the implementation, management and operation of computerised systems. Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-Operation Scheme (PIC/S) has provided recommendations and background information concerning computerized systems that will be of assistance to inspectors for training purposes and during the inspection of computerized systems.

II. WORLD’S LEADING DRUG REGULATORY AGENCIES

The country specific drug agencies formulate and inspect the guidance related to GMP, in addition to international bodies like World Health Organization (WHO), the Pharmaceutical Inspection Cooperation/Scheme (PIC/S), and the International Conference on Harmonization (ICH).

| S. No | Country | Agency | Important Guidelines |
|-------|----------------|--|--|
| 1. | United States | United States - Food and Drug Administration (USFDA) | 21 CFR Part 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs 21 CFR Part 211 - Current Good Manufacturing Practice For Finished Pharmaceuticals |
| 2. | United Kingdom | Medicines and Healthcare products Regulatory Agency (MHRA) | Good Manufacturing Guide , Orange Book |
| 3. | Brazil | Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil)-ANVISA | Good Manufacturing Practices |
| 4. | Australia- | Therapeutic Goods Administration | Australian Code of Good Manufacturing Practice for Medicinal Products |



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| 5. | Canada | Health Canada | Canadian Good Manufacturing Practices for Drugs (Part C Division 2 of Food and Drug Regulations) |
| 6. | China | Drug Administration Law of the People's Republic of China | Regulations for Implementation |
| 7. | World Health Organization | WHO | Technical Report Series (TRS), Good Manufacturing Practices |
| 8. | European Union | European Medicines Agency | Eudralex Volume 4 - Good Manufacturing Practice Guidelines Directive 2003/94/EC for medicinal products for human use and investigational medicinal products for human use |
| 9. | India | Central Drug Standard Control Organization | Schedule M - Good Manufacturing Practices and Requirements of Premises, Plant and Equipment For Pharmaceutical Products |
| 10. | Japan | Pharmaceuticals and Medical Devices Agency | Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs |

III. SIX BASIC CONTROL SYSTEMS

Each of drug regulatory bodies across the world aspire practices to encourage and assist hightech industries. Risk based prioritization in manufacturing inspections should instigate risk-based evaluation -making on a practical, each unit operation level throughout the manufacturing business. Implementation of the comprehensive 'Quality System Model' would ensure greater understanding of total operations leading to a more robust and updated Quality System that is fully compliant with cGMP regulations.

The quality system provides the foundation for the manufacturing systems that are linked and function within it.

- a. Quality System
- b. Facilities and Equipment
- c. Materials
- d. Production
- e. Packaging and Labeling
- f. Laboratory Control and Operations



The diagram shows the correlation ship amongst the six systems: the quality system and the five manufacturing systems, which appear to be closely interrelated and inseparable during operations.

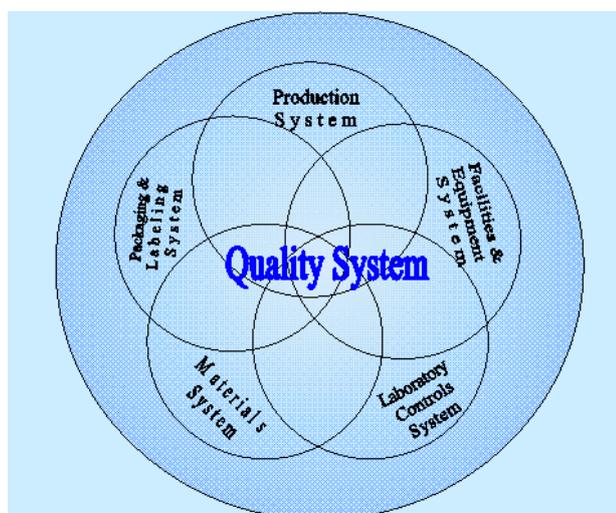


Figure-1, Six-system Inspection Model as per USFDA

The concepts of GMP do not treat the five manufacturing systems as discrete entities, but instead integrates them into appropriate sections interlinked with each other. The interrelationships between processes should be quite apparent. One of the important themes of the systems-based inspection compliance program is to be able to assess whether each of the systems is in a state of compliance. Pharmaceutical manufacturers should implement modern quality systems with risk management approaches to meet the requirements of the Agency's current good manufacturing practice (cGMP) as per regulations (21 CFR parts 210 and 211). The guidance based on comprehensive quality systems (QS) model, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs shall be of great help.



IV. BASIC REQUIREMENTS OF GMP

There are a number of provisions and procedures are implemented as a part of Good Manufacturing Practices (GMP) but following are the bare minimum requirement to ensure consistent quality of pharmaceutical products.

Ten Points GMP basic requirements can be summarized follows:

1. Manufacturing processes and sub-processes are clearly defined, documented and controlled to ensure consistency and compliance with approved specifications
2. Each critical steps of manufacturing processes and significant changes to the process are validated prior to commercialization of products
3. All necessary key elements for GMP are provided, including the following
 - i. personnel are qualified and trained (or suitable combination of these two)
 - ii. adequate premises and space with suitable surroundings
 - iii. suitable equipment and supporting services,
 - iv. correct materials, closure system, containers and labels
 - v. approved specification procedures and instructions,
 - vi. proper product storage and transport.
4. Instructions and procedures are described in clear and unambiguous language
5. Operators and personnel are trained to carry out and document procedures;
6. Records are online made during manufacture that demonstrate that all the steps required by the defined procedures and Deviations are investigated and documented
7. 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
8. Control of storage, handling, and transportation of the drugs minimizes any risk to their quality through adequate systems like Quality Risk Management
9. Well documented system is available for recalling of drugs from sale
10. Product 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.

For supporting above basic requirement, following procedures and concepts as per regulatory guidance must be implemented by pharmaceutical manufacturers:

- ✓ Process Validations (PV)
- ✓ Handling Out of Specification (OOS)
- ✓ Quality Risk Management (QRM)
- ✓ Process Analytical Techniques (PAT)



- ✓ Corrective Action and Preventive Actions (CAPA)
- ✓ Change Control and SUPAC

V. CONCLUSION

There is significant amount of overlap between the elements of a quality system and the cGMP regulation requirements for manufacturing operations. Quality by design means designing and developing manufacturing processes during the product development stage to consistently ensure predefined quality at the end of the manufacturing process.

Numerous controls are exercised by pharmaceutical manufacturer, but GMP fundamentally assures the stakeholders about mitigating following quality risks:

- ✓ Cross-contamination
- ✓ Mix-ups
- ✓ Not of Standard Quality (NSQ)

Each drugs regulatory agency has expectations from manufacturer's commitment towards at least following aspects for successful GMP:

- ✓ Good professional practice and quality of testing, validation and risk based approach
- ✓ Self-Inspection and Compliance with Good Practices on consistent basis to enable the facility for all time readiness for regulatory inspection.

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