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COMPREHENSIVE QUALITY MANAGEMENT SYSTEM FOR REGULATORY COMPLIANCES

Jadhav Pratiksha S., Bhusnure Omprakash G.*, Gholve Sachin B., Shital Chakure S.

***Department of Quality Assurance, Channabasweshwar Pharmacy College (Degree), Kava Road, Basweshwar Chowk, Latur, Maharashtra, India-413512**

***Corresponding Author Email:** omprakashbhusnure@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.
The FDA has enacted several pharmaceutical cGMP regulations. These are key concepts that are critical to quality systems. Some of the concepts by which the FDA and other regulatory bodies ensure cGMP regulations are Quality, Quality by Design (QbD) and product development, Quality Risk Management, Corrective and Preventive Action (CAPA), Change Control, and the Six Systems Approach Of these, the six-system inspection approach is a systems-based approach to cGMP and is aimed at ensuring a robust quality system model for pharmaceutical products.

KEY WORDS

Quality Management System, CGMP, ICH, USFDA, WHO

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.
This guidance is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (2l CFR parts 210 and 211). The

guidance describes a comprehensive quality systems (QS) model, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. The guidance also explains how manufacturers implementing such quality systems can be in full compliance with parts 210 and 211. This guidance is not intended to place new expectations on manufacturers, nor to replace the CGMP requirements. Readers are advised to always refer to parts 210 and 211 to ensure full compliance with the regulations.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required. [1-4]

United States Food and Drug Administration (USFDA) in September 2004 announced pharmaceutical Current Good Manufacturing Practices (CGMP) for 21st century [5] The intention was to integrate quality system and risk management with existing CGMP guidelines to encourage adopting modern and innovative manufacturing technology. Also, to harmonies the USFDA CGMP regulatory requirement with other international CGMP regulatory requirement [6-7]and other quality management systems like International Standard Organization (ISO-9000) etc. The concept of Comprehensive Quality Management System (CQMS) is emerging from the USFDAs pharmaceutical CGMP for 21st century. The material in this paper is interpreted by the author from the Draft guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations [5]

Here, USFDA propose Six System Inspection Model for Food and Drug Administration (FDA) personnel for conducting inspection. By referring this model, we developed Eight System Inspection Model which is a part of CQMS from the auditor and audited or pharmaceutical organization point of view. It consists of two more systems i.e. regulatory/management and engineering. Here, we consider quality system as separate section which comprises the quality assurance and other quality related aspects. This system covers not only the 20 points referred by USFDA but also the other important aspects of CGMP i.e. 21 Code of Federal Regulations (CFR) Parts 210 & 211. [5-7]

- **Six system approach to pharmaceutical CGMP Regulations**

The FDA has enacted several pharmaceutical cGMP regulations. These are key concepts that are critical to quality systems. Some of the concepts by which the FDA and other regulatory bodies ensure cGMP regulations are Quality, Quality by Design (QbD) and product development, Quality Risk Management, Corrective and Preventive Action (CAPA), Change Control, and the Six Systems Approach. [8]

Of these, the six-system inspection approach is a systems-based approach to cGMP and is aimed at ensuring a robust quality system model for pharmaceutical products. Each of drug regulatory bodies across the world aspire practices to encourage and assist high-tech 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 Mode would ensure greater understanding of total operations leading to a more robust and updated Quality System that is fully compliant with cGMP regulations.

- **Six system models [9-10]**

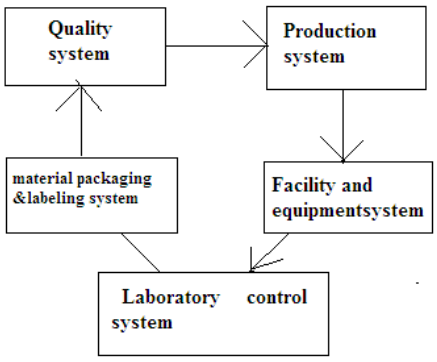

Fig. 1: Six system model

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.

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 (2l 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.

1. **Quality System:**

This system assures overall compliance with cGMPs and internal procedures and specifications. The system includes the quality control unit and all of its review and approval duties (e.g. change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.). It includes all product defect evaluations and evaluation of returned and salvaged drug products. See the cGMP regulation, 21 CFR 211 Subparts B, E, F, G, I, J, and K.

2. **Facilities and Equipment System:**

This system includes the measures and activities which provide an appropriate physical environment and resources used in the production of the drugs or drug products.

It includes:

a) Buildings and facilities along with maintenance;

b) Equipment qualifications (installation and operation); equipment calibration and preventative maintenance; and cleaning and validation of cleaning processes as appropriate. Process performance qualification will be evaluated as part of the inspection of the overall process validation which is done within the system where the process is employed; and,

c) Utilities that are not intended to be incorporated into the product such as HVAC, compressed gases, steam and water systems. See the cGMP regulation, 21 CFR 211 Subparts B, C, D, and J.

3. **Materials System**: This system includes measures and activities to control finished products, components, including water or gases, that are incorporated into the product, containers and closures. It includes validation of computerized inventory control processes, drug storage, distribution controls, and records.

See the cGMP regulation, 21 CFR 211 Subparts B, E, H, and J.

4. **Production System:** This system includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures. See the cGMP regulation, 21 CFR 211 Subparts B, F, and J.

5. **Packaging and Labeling System**: This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations. See the cGMP regulation, 21 CFR 211 Subparts B, G, and J.

6. **Laboratory Control System**: This system includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program. See the cGMP regulation, 21 CFR 211 Subparts B, I, J, and K.

- **The Six Subsystems of a Pharmaceutical Quality System**

Risk taking is an important part of any business endeavor. Entrepreneurs and investors take risks every time they fund a start-up. Business executives take risks every day as they make decisions about which products, services, ideas and people to advance within an organization. Risk taking can be enormously profitable. Based on the latest guidance from the FDA, an effective pharmaceutical quality system should help ensure compliance with cGMPs by focusing on:

- Quality management
- Quality assurance

- Evaluation analysis and quality risk management tools
- Preventive action
- Risk management
- Continuous improvement

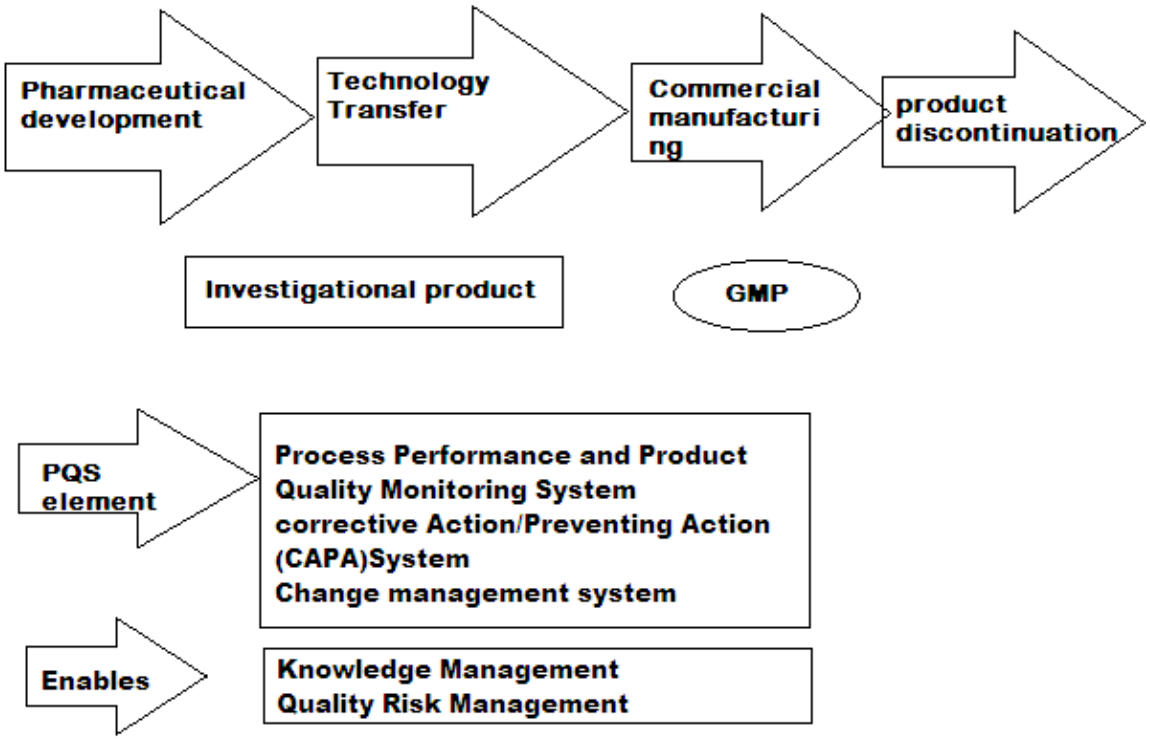

Fig No.2: Six subsystem of pharmaceutical quality system

- **SEVEN CRITICAL CONCEPTS**

The guidance identifies seven concepts critical for modern quality systems:

1. **Quality:** Refers to the strength, purity, and other quality characteristics meant to ensure a drug product's safety and effectiveness.
2. **Quality by Design and Product Development**: Designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality. [11]
3. **Quality Risk Management:** This includes assessing the risks of quality issues, selecting and implementing risk management controls commensurate with the level of risk, and evaluating the results of the risk management efforts. [12]
4. **Corrective Action and Preventive Action (CAPA):** Focuses on investigating, understanding, and correcting discrepancies while trying to prevent their recurrence. Quality system models discuss CAPA as three separate concepts, all of which are used in this guidance
   a. Remedial corrections of an identified problem
   b. Root cause analysis with corrective action to help understand the cause of the deviation and potentially prevent recurrence of a similar problem
   c. Preventive action to avert recurrence of a similar potential problem

5. Change Control: Managing change to prevent unintended consequences.

6.Quality Unit: A group within an organization that promotes quality in general practice. [13]

Current industry practice generally divides the responsibilities of the quality control unit (QCU), as defined in the CGMP regulations, between quality control (QC) and quality assurance (QA) functions.

- QC usually involves

(1) Assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products;

(2) Evaluating the 6 See ICH Q9 Quality Risk Management. 5 Contains Nonbinding Recommendations performance of the manufacturing process to ensure adherence to proper specifications and limits; and (3) determining the acceptability of each batch for release

- QA primarily involves

(1) Review and approval of all procedures related to production and maintenance,

(2) Review of associated records, and

(3) Auditing and performing/evaluating trend analyses.

- **Basis of C.Q.M.S.: -**

It is based on the philosophy that,

"Quality should be built into the product and testing alone cannot be relied on to ensure product quality."

This statement is supported by one incident which was happen with Boehringer Knoll Laboratories Ltd. There was production of an Antibacterial drug containing active ingredient as antibacterial agent along with other excipients. But due to failure in dispensing practice the dispensing officer dispensed Glibenclamide as one of the excipients along with antibacterial agent. In final Quality Control testing all test parameters were acceptable. But the incident of wrong addition of Glibenclamide came in focus, only after the complaints related to hypoglycemic effect are reported. This incident gives an idea that there are lots of such parameters which could not ensure the quality of product only by the final testing. That means the quality should be built throughout the material and process flow and not only by the final testing of the product.

- **FDAs 20 Points**

1. Provide leadership

In developing robust quality management system, the higher authority or senior management has to define organizations mission and strategies. They have to take active participation in system design, implementation, monitoring and review, committing necessary resources visibly support the quality system. They have to develop internal communication in the area of research development, regulatory affairs, manufacturing, quality unit, personnel and other related issues.

***2.* Structure the organization**

When designing a CQMS, the management has the responsibility to define organizational structure and document it and also to determine the jobs (employee roles), responsibilities and authorities within the system, to empower employee to detect and resolve the problems affecting quality of product.

***3.* Build your quality system to meet requirement**

The CQMS provide system help to ensure compliance within the regulations related to identity, strength, safety, purity and efficacy, to control the outsourcing. It also defines standards of quality (specifications) and implementation of quality policies. The developing, implementing, monitoring and revising quality procedures is one of the major aspects of CQMS

***4.* Establish policies, objectives and plans**

In developing CQMS, the senior management articulates their vision of quality through implementing the policies, objectives and plans. They provide strong commitment to quality into the organizational mission. They are responsible for developing quality manual, quality policies and to communicate policy at all levels of the organization, to make all employees and all other relevant people to understand it in letter and spirit also to revise these policies as and when needed.

The Quality objectives are created at the top level of the organization (and other level as needed) through a formal quality planning process. Use quality planning process to identify resources and define methods to achieve the quality objectives.

5. Review of the system

System review is required to continuing suitability, adequacy and effectiveness of the robust quality system. Such review should typically include both, an assessment of the product as well as customer needs. The quality system review should cover the points like, quality policy and objectives, result of audit and other assessment, customer feedback including complaints, trend analysis, actions to prevent a potential problem or a recurrence, follow up action from previous management reviews.

The review result must be recorded, planned actions should be implemented using corrective and preventive action and change control procedures.

6. General arrangements of resources

The following resources should be provided in adequacy,

1. Building and facilities
2. Equipment
3. Materials
4. Defined manufacturing and packaging process
5. Facilities for laboratory analysis and related resources

7. Develop personnel

The CQMS recommends qualified and trained personnel to do an assigned work properly, without overruling the CGMP regulations.

The training programmers should include at least following points,

1. Identification of training needs
2. Provision for training to satisfy their needs.
3. Evaluation of effectiveness of training
4. Documentation of training and retraining
5. Use of skills learned in training, in day to day activities.

8. Facilities and equipment

FDA officer's expertise can be used to identify and select the proper facilities and equipment. (Pre-inspection approval may be sought). These facilities and equipment must be qualified, calibrated, cleaned and maintained to prevent contamination and mix-ups. Equipment should include both process as well as testing equipment's i.e. manufacturing, utilities and testing instruments or equipment's etc.

9. Control outsourced operations

While outsourcing for operational processes to a second party, the Quality agreement should clearly describe materials and services, quality specifications responsibilities and communications mechanisms. Contract giver should satisfy himself about the adequacy and ability of the contract acceptors in terms of his quality systems and its implementation.

10. Design and development of product and processes

In CQMS the product characteristics are defined from design to delivery and exercise change control, and also the manufacturing, quality process and procedures are defined. It also establishes responsibilities for designing or changing products, documenting processes will ensure that critical variables are identified. This document should include resources and facilities needed, procedures to carry out processes, identification &control of critical variables, validation activities including operating ranges and acceptance criteria etc.

11. Monitor packaging and labeling processes

The CQMS recommend planning and documentation of all packaging and labeling procedures. These Procedures should outline Quality Control (QC) activities and responsible position, specifications and controls for packaging and labeling materials should also be determined before commercial production.

In CQMS, a design plan should include authorities and responsibilities; design and development stages; and appropriate review, verification and validation. Change control should be maintained throughout the design process.

12. Examine inputs

In CQMS models, the term "input" refers to any materials that goes into a final product, no matter, whether it is traceable or not in the finished product and also whether the materials is purchased by the manufacturer or produced by the manufacturers for the purpose of processing. Materials can include items such as components (e.g. ingredients, process water etc.container and closures etc. Quality system should address receipt, production, storage and use of all products.

13. Perform and monitor operations

In the CQMS, areas of process weaknesses should be identified and factors that are influential on critical quality attributes should receive increased scrutiny. The process should be validated, and sufficient testing data should be provided a system for continuous improvement of operations should be developed and implemented. The entire life-cycle should be addressed by the establishment for continuous improvement mechanism in the CQMS

The critical Process parameters monitored during production are as follows

1. Process step should be verified by using validated computer system or a second person; these records must be maintained simultaneously.
2. Procedures should be in place to prevent objectionable microorganisms in finished product that is not required to be sterile and to prevent microbial contamination of finished product purported to be sterile, sterilization process should be validated.
3. The procedure should be developed to monitor, measure and analyses the operations
4. Procedure should be in place to ensure the accuracy of test result.
5. The system should address how to deal with "Out of Specifications" results.
6. The CQMS should address product distributions issues.

14. Address non-conformities

A key component in any CQMS is handling of non-conformities / or deviations. It includes,

1. Defining and classifying non-conformities (e.g. Critical, Major & Minor)
2. Developing document system for identifications, investigation and corrective action to be taken against non-conformities.
3. Planed action for remedial purpose to avoid the recurrence in future and segregation of product currently facing non-conformities.

15. Analyze data for trends

It involves collecting data from monitoring, measurement, complaint handling and other activities. This information is useful for detection and prevention of problems as early as possible.

16. Conduct internal audits

CQMS approach call for audits to be conducted at planned intervals to evaluate effective implementation and maintenance of the quality system and to determine if processes and products meet established parameters and specification.

The entire system should at least be audited once the year in staggered or planned manner. The managers who are responsible for the areas audited to take timely actions to resolve audit findings and ensure that follow up actions are completed, verified and recorded.

17. Risk assessment

The management should assign priorities to activities or actions based on the consequence of actions or inaction otherwise known as risk assessment. The risk assessment is used as a tool in the development of product specifications and critical process parameters used in conjunction with process understanding, risk assessment helps anticipated, manage and control change.

18. Corrective action

The corrective action is a reactive tool for a system improvement to ensure that significant problems do not occur. The procedure is to be developed and documented to ensure that the need for action is evaluated relevant to the possible consequences, the root cause of the problem is investigated, possible actions are determined, selected action is taken within the defined time frame and effectiveness of the action taken is evaluated. It is essential to maintain records of corrective action taken. The management can gather information from following sources for taking corrective action,

a. Nonconformance report and rejection
b. Complaints
c. Internal and External audit
d. Data and risk analyses related to operation and quality system processes
e. Management review decisions

19. Preventive action

The preventive action is an essential tool in quality system management.

The Preventive action may involve areas like, succession planning, training, capturing institutional knowledge, planning for personnel, policy and process changes. The selected preventive action should be evaluated and recorded, and the system should be monitored for the effectiveness of the actions.

20. Promote improvement

The effectiveness of the quality system can be improved through the quality activities described as above in CQMS. It is critical that senior management be involved in the evaluation of this improvement process.

- **QMS in Pharmaceutical industry**

1. QM Tools

A} Check sheet

The check sheet is form used to collect data in real time at the location where the data is generated. The data is captures can be quantitative or qualitative. When the information is quantitative the check sheet is sometimes called tally sheet.

B} Control chart

Control chart also known as Shewhart charts or process behavior charts in statistical process control are tools used to determine if a manufacturing or business process is in a state of statistical control.

C} Pareto chart

A pereto chart named after vilfredo Pareto is a type of chart that contains both bars and line graph, where individual valves are represented in descending order by bars and cumulative total is represented by the line.

D} Scatter plot method

It is a type of mathematical diagram using Cartesian coordinates to display valves for two variables for a set of data. The data is displayed as a collection of point each having the value of

one variable determining the position on horizontal axis and value of other variable determining the position on

vertical axis . This kind of plot is also called a scatter chart, scatter gram, scatter diagram.

E} Ishikawa diagram

Ishikawa diagram (also called fishbone diagram, herringbone diagram cause and effect diagram) are causal diagrams created by Ishikawa (1968) that show the cause of specific event. Common uses of Ishikawa diagram are product design and quality defect prevention to identify potential factors causing on overall effect.

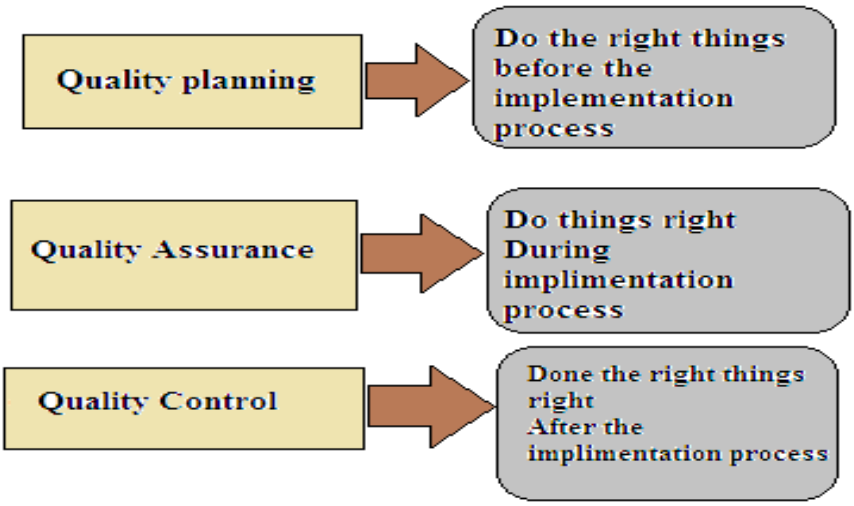

Fig No.3 Ishikawa diagram

- **Eight principles of ISO quality management system**

The International organization for Standardization (ISO) outlines eight quality management principles called ISO 9000 series of standardization.

1. Customer focus

Pragmatically, a quality product centers on meeting customers current and future requirements in the needed form, time, and place in synchrony with company policies and objective.

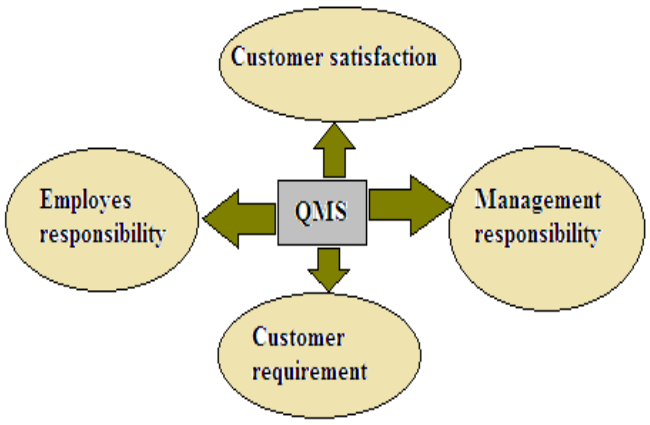

Fig no. 4 Customer focus

2. Leadership

Application

1. Perfect understanding of the organization short and long tern goals and objective.
2. Setting realistic and practicable targets
3. Make the needs of all stakeholders o focal point
4. Positive contributions must be encouraged

Benefits

1. More enthusiastic workers
2. Increased employee loyalty
3. Effective communication system is enable

3. Involvement of people

Application

1. A sense of belonging should be created in people that has direct and indirect link with the company
2. People should be made to understand that their opinion counts
3. People openly discussing problems and issues
4. People identifying constraints to their performance.

Benefits

1. Employees show more commitment towards achieving organization goals and objectives.
2. Innovation and creativity within organization
3. People show more interest in continuous improvement

4. Process approach

Continual improvement of quality management system

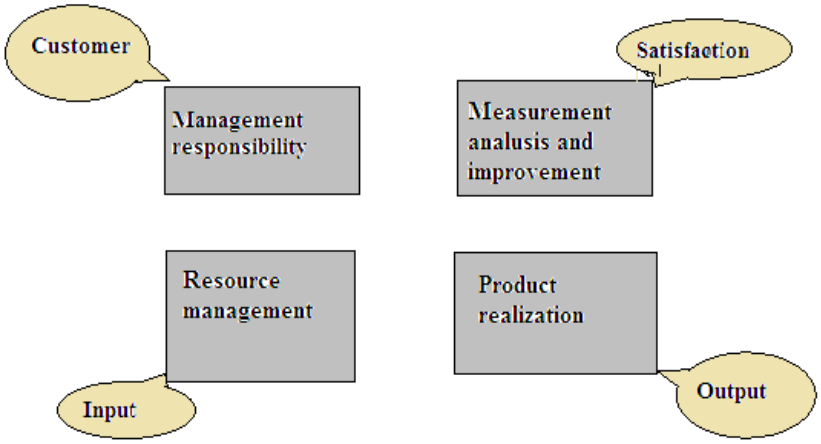

Fig No.5 Process Approach

5. Continuous improvement

Benefits

1. Performance advantage through improved organizational capabilities
2. Alignment of improvement activities at all levels to an organizations strategic intent.
3. Flexibility to react quickly to opportunities.

6. System approach to management

System = combinations of entities that works dependently and interrelated with each other and becomes a culture over a period of time.

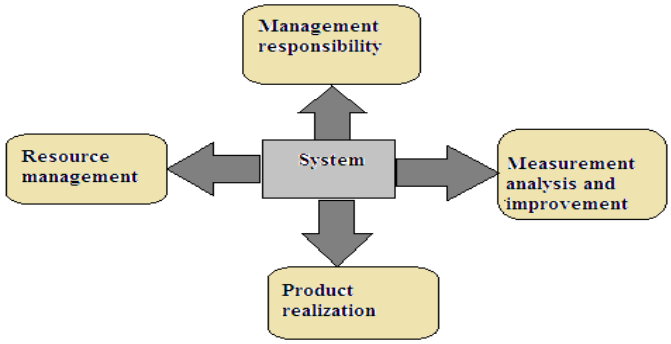

Fig No. 6 System approach management

7. Factual approach to decision making

Benefits

Prevents impulsive decision making that could dissatisfy majority of the customers

An increasing ability to demonstrate the effectiveness of past decision through reference to factual records.

Only informed decision will be made generically.

8. Mutually beneficial supplier relationships

Benefits

1. Increasing ability to create value for both parties
2. Optimization of costs and resources

- **Benefits of Inspection**
  1. Minimize risk
  2. Avoid expensive re-inspection
  3. Reduce costs and improve acceptance of goods internationally
- **QMS challenges**
  1} Challenges in problem identification
  2} Challenges in investigation
  a) Identify and investigate root cause
  3} challenges in planning
  a) Vague of root cause analysis
  b) Lack of integration to change control system
  c) Confusion over what is corrective and what is preventive action.
- **Authors Points**

1. Validation

Initially pharmaceutical industry was heavily depended on controlling the quality, over a period of time this concept has changed to assuring the quality of product [7]

Pharmaceutical validation is the major activity under the quality assurance. Validation assures the desired performance of,

- Buildings
- Equipment
- Materials
- Processes etc

Hence, without validation we cannot think of assuring desired quality attributes in any product.

***2.* Heating, Ventilation and Air conditioning (HVAC) system validation**

Air is one of the major constituent in the creating the desired environment including storage and processing. This environment includes requirements related to temperature, relative humidity, class of air, differential pressure; number of air changes etc. and this entire thing is taken care by a suitably designed, operated, monitored and maintained HVAC system.

***3.* Water and steam system validation**

All the regulatory requirements including pharmacopoeia monographs give lot of importance to quality of pharmaceutical water. Particularly USP, not only describes different monographs on pharmaceutical water, but also describes in detail validation system for pharmaceutical water. Pharmaceutical water is to be considered as one of the major raw materials particularly in case of most of the liquid formulations either sterile or non-sterile.

4. Vendor certification

USFDA and other drug regulatory authority's world over insist on consistency of quality of all the inputs into manufacturing of pharmaceutical product or hence, certification of vendors becomes a very important activity in assurance of quality of pharmaceutical product. One can depend on certified vendors for consistency of quality, commitment of deliveries and other technical & commercial aspects related to purchase of inputs.

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:

1 Cross-contamination
2 Mix-ups
3 Not of Standard Quality (NSQ)
4 Each drug regulatory agency has expectations from manufacturer's commitment towards at least following aspects for successful GMP:
5 Good professional practice and quality of testing, validation and risk-based approach
6 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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***Corresponding Author:**
Bhusnure Omprakash G*
Email: omprakashbhusnure@gmail.com