International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

A Review: Pharmaceutical Quality Management Systems (TQM, CFR 21 part 11, ICH Q10, WHO-GMP Requirements, Six Sigma)

Miss. Sakshi G. Bhandwalkar[1], Miss. Manali S. Bhopate[2], Mr.Swapnil S. Khopade[3], Mrs. Vaibhavi V. Kunjir
Institute Name: Rajgad Dyanpeeth's College Of Pharmacy, Bhor

Submitted: 11-03-2024 Accepted: 21-03-2024

ABSTRACT :
Pharmaceutical industry is most widely manufacturing unit. Quality management system can affect the quality of the in process or finish product. The focus of this paper is to highlight the pharmaceutical quality management system such as Total quality management, ICH Q10 guidelines, CFR-21 part 11, WHO GMP- Requirements and Six sigma. TQM is the latest system in the quality management where all activities all focus at optimizing customer satisfaction through the continuous improvement. The International Council for Harmonization (ICH) "Q10 Pharmaceutical Quality Systems" (ICH Q10) guidance was introduced to address the growing gap between current good Manufacturing practices and pharmaceutical manufacturing quality systems. Code of Federal Regulations (CFR) Title 21 Part 11, focusing on its impact on electronic records and signatures within the realm of regulated industries, particularly the pharmaceutical, biotechnology, and medical device sectors. CFR 21 Part 11 establishes the criteria under which electronic records and signatures are considered trustworthy, reliable, and equivalent to paper records. Pharmaceutical Quality Management, focusing on the integration of Total Quality Management (TQM), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q10 guideline, and the Code of Federal Regulations (CFR) Title 21 Part 11. The pharmaceutical industry's commitment to ensuring product quality and patient safety has led to the adoption of robust quality management systems. The review explores the key principles of TQM and its application in the pharmaceutical context, emphasizing continuous improvement, customer focus, and employee involvement. Additionally, the article delves into the ICH Q10 guideline, elucidating its role in establishing a pharmaceutical quality system that covers the entire product lifecycle. A critical analysis of CFR-21 Part-11 is included, highlighting its significance in the context of electronic records and signatures. The synthesis of TQM, ICH Q10, and CFR-21 Part-11 principles is examined to provide insights into how these frameworks collectively contribute to enhancing pharmaceutical quality and compliance. The article discusses case studies and practical applications, shedding light on successful implementation strategies and challenges faced by the industry.
By consolidating these key elements, this review aims to offer a comprehensive understanding of the interconnected facets of pharmaceutical quality management, providing stakeholders with valuable insights for navigating the complex regulatory landscape and ensuring the delivery of safe and effective pharmaceutical products.

Key Words : Pharmaceutical Quality Management Systems, Total Quality Management, ICH Q-10, CFR 21- part-11, WHO-GMP Requirements, Six-Sigma System.

I. INTRODUCTION:

In the worldwide marketplace levels of competition have been increased, resulted in increasing importance of quality of organization and consequently Total Quality Management (TQM) has become a core management issue . In progressive years Total Quality Management (TQM) has gain worldwideattention and is being accepted inmanyindustries, particularly in advanced economies. TQM has developed because of the changes in worldwide economy . Total quality management was first introduced by Dr. W. Edwards Deming in the years 1950 . Total Quality Management is a management approach aimed at continuous improving the quality of product, service and process within an organisation. It involves a comprehensive set of principles, practices and techniques focused on meeting and exceeding customer expectations. TQM emphasizes a commitment to quality by involving every level and function within a organisation, fostering a culture of continuous improvement,

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

teamwork and customer satisfaction. TQM includes improve quality in a pharmaceutical products as it comprises complete records such as standard operating procedures for every step, validation records, master formula record and batch production records, etc. This review involve quality, quality management, newer status and need of TQM.

Historical overview of TQM :

TQM has its roots in the post- world war 2 era , particularly in Japan. Influential figures like W.Edward Deming and jaseph M.juran played pivotal roles in shaping it's early principles .Deming introduced statistical method for quality control and emphasized the importance of management involvement in quality improvement.Juran contributed concepts like the pareto principle , quality trilogy and quality improvement. A new chapter of quality control and management began in the year 1980s and quality management.

Benifits :

- Enhanced customer satisfaction
- Total change in organization working culture
- Increased productivity and efficacy
- Incorporation of advanced production techniques
- Devlopment of new products and skills
- Enhanced teamwork
- Reduced inventory
- Increased profitability

Characteristics of TQM:

- A sustained management commitment to quality
- focus on the customer
- preventing and detecting defects
- Universal quality responsibility
- Quality measurement
- continuous improvement
- Root cause corrective actions
- Employee on teamwork
- strategic thinking
- Benchmarking
- Training
- supplier teaming

Principle of TQM :

Implementing TQM is a strategic decision that requires commitment from top management and the entire workforce. When effectively executed, it can lead to sustained improvements in quality, productivity, and overall organizational performance.

Feel free to delve deeper into each subsection by providing specific examples, case studies, or statistics that highlight the significance and practical implications of TQM in various industries or contexts.

PDCA Cycle (Demings Cycle) :

Deming introduced the shewhart cycle (PDSA) as an important structure to show improvement for quality and productivity. He developed four steps for improvement i.e Plan-Do-Check-Act are known as PDCA Cycle. Currently PDCA Cycle significantly apply in development and deployment 9f the quality policies. Moreover, management system standards such as ISO 9091 can improve productiveness of the processes of organization through Plan-Do-Check-Act (PDCA) method to acquire the successful satisfaction of the customer and quality .

Fig 1 : PDCA Cycle

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

6 Cs of Total Quality Management :

1. Commitment :

If a TQM culture is to be enlarge, so that quality improvement becomes everyone's duty , a clear commitment , from te top must be prepared. Without this al the procedure becomes fails. It is not enough to represent quality issues to a single employee since this will not provide an environment for changing attitudes and breaking down the barriers to quality improvement. Such expectations must be made clear toghether with ths support and training neccesary to their achievement.

2. Culture :

Training lies at the centre of effecting a change in culture and attitudes. Management accountants, too often associate 'creativity' with 'creative accounting' and associated negative perceptions. This must be changed to encourage individual contributions and to make 'quality' a normal part of everyone's job.

3. Continuous improvement:

Recognition that TQM is a 'process' not a 'programme' necessitates that we are committed in the long term to the never- ending search for ways to do the job better. There will always be room for improvement, however small.

4. Co-operation:

The application of Total Employee Involvement (TEI) principles is paramount. The on-the-job experience of all employees must be fully utilised and their involvement and co-operation sought in the development of impro strategies measures.

5. Customer focus:

The needs of the customer are the major driving thrust; not just the external customer (in receipt of the final product or service) but the internal customer's (colleagues who receive and supply goods, services or information). Perfect service with zero defects in all that is acceptable at either internal or external levels. Too frequently, in practice, TQM implementations focus entirely on the external customer to the exclusion of internal relationships; they will not survive in the short term unless they foster the mutual respect necessary to preserve morale and employee participation.

6. Control:

Documentation, procedures and awareness of current best practice are essential if TQM implementation are to function appropriately. The need for control mechanisms is frequently overlooked, in practice, in the euphoria of customer service and employee empowerment. Unless procedures are in place improvements cannot be monitored and measured nor deficiencies corrected. Difficulties will undoubtedly be experienced in the implementation of quality improvement and it is worthwhile expounding procedure that might be adopted to minimise them in detail.

Pharmaceutical Quality Management ICH Q10

ICH :

ICH is joint venture involving both regulatory and research based industry initiatives from Europe, Japan, and United States for scientific and technical discussion of the test process; It needs to be evaluated and verified Safety, Quality and Efficacy of medicines. ICH stands for "International Conference on Harmonization" of Technical requirements for registration of pharmaceuticals for human use. ICH was established in 1990 as a joint through regulatory/ industrial projects for improvement harmonization, process efficiency, for develop and register new drugs products from Europe, Japan and United States. Provide medicinal products to them patients with minimum delay.

Manufacturing science has made recent advances and continues to grow an understanding of the positive impact of quality system throughout the pharmaceutical industry. This includes the need for guidance from regulatory authorities on appropriate implementation and maintenance practices for pharmaceutical quality system. This need is currently meet through individual projects of regulatory bodies such as United States Food and Drug Administration (FDA) cGMP Pharmaceuticals for 21st century initiative. In addition, International harmonization efforts have been made this need, as observed by the international council of harmonization (ICH) and International Standards for Organization (ISO) guidance documents regarding pharmaceutical quality system.

History of ICH :

EU harmonization initiatives regulatory requirements in the 1980s, At the same time, a bilateral discussion was held between then on the possibilities of Europe, Japan and United States

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

harmonization in WHO conference on medicine regulatory authority, in Paris, in 1989. Specific plans for action began to materialize. Official of the IFPMA (International federation of pharmaceutical manufacturers and association) to discuss joint regulatory industry initiatives on International harmonization and ICH were conceptualized. ICH was developed in meeting in April 1990, EFPIA (European federation of pharmaceutical industries and association) in Brussels.

Goals of ICH :

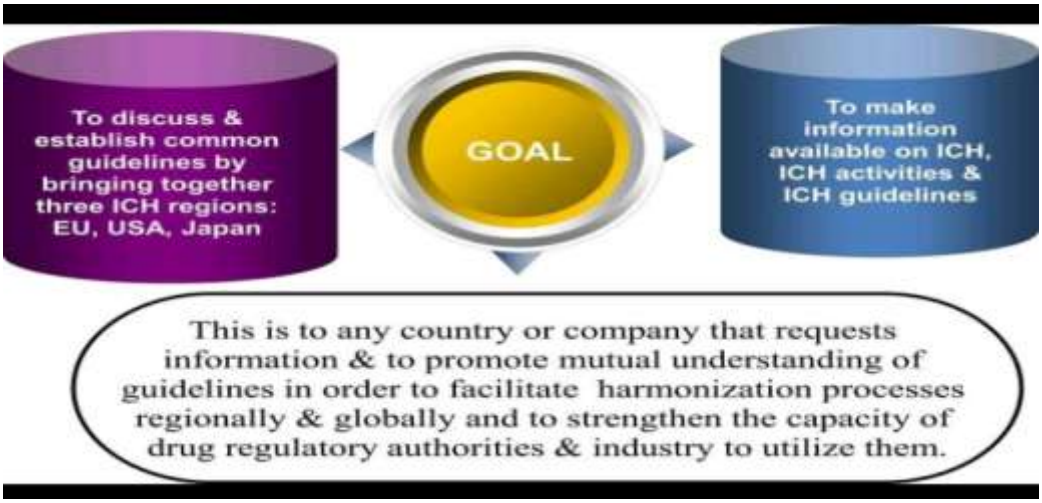

Fig 2 : Goals of ICH

ICH Guidelines :

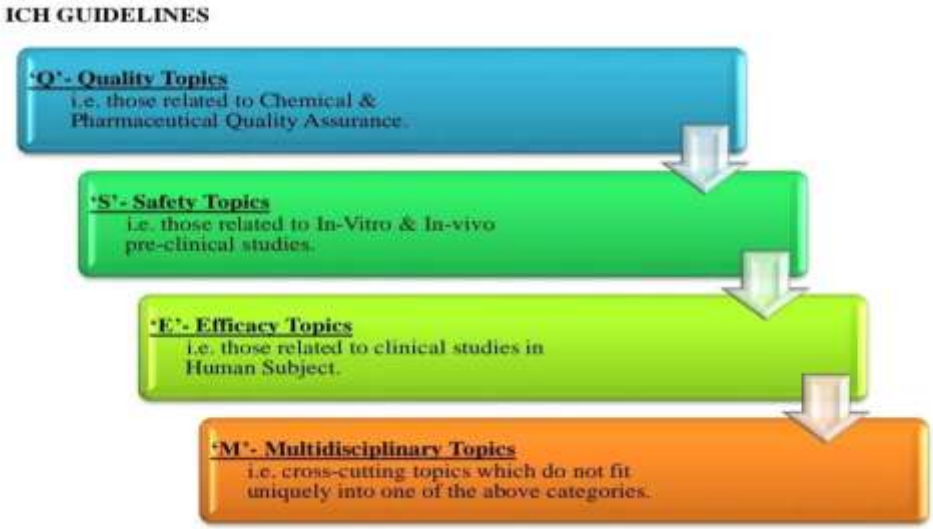

Fig 3 : ICH Guidelines

Pharmaceutical Quality Management:

ICH Q10 pharmaceutical quality system (PQS) is a guideline that defines an effective quality management system model for the pharmaceutical industry. ICH Q10 provides a comprehensive model based on the quality concepts of the International Organisation for standardization (ISO). It also covers relevant Good Manufacturing Practices (GMP) regulations. The purpose of this directive is to ensure that a robust quality system is established to support the consistent production of safe and effective pharmaceutical products. These systems control important processes such as formula development drug manufacturing, quality control, change management systems, CAPA system and others. Other life sciences companies that have adopted ICH Q10 include pharmaceutical and

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

biotechnological manufacturers and contract research organisations.

Fig 4 : Elements and Enablers of PQM

Objectives :

Implementation of the Q10 model should result in achivement of three main objectives which enhance regional GMP requirements.

1)Achieve product realization :

Establishes, implements and maintains systems that enable the delivery of quality products appropriate properties to meet the needs of patients, health professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.

2)Establish & maintain state of control :

Developing and using effective monitoring and control systems for process performance and production Quality, which guarantees the continuous adaptability and capacity of the processes. Quality risk Management can be useful in identifying monitoring and control systems.

3)Facilitate continual improvement :

Identify and implement appropriate product quality improvements, process improvements,It reduces variability, increases innovation and improvement of the pharmaceutical quality system Ability to consistently meet quality requirements. Quality risk management can be useful in identifying and Prioritize areas for continuous improvement.

Scope:

These guidelines apply to systems that support the development and manufacture of pharmaceuticals Drug substances (ie APIs) and drug products, including biotechnology and biological products, Throughout the product life cycle.

There are four stages of guidelines:

1)Pharmaceutical development
2)Technology transfer
3)Commercial manufacturing
4)Product discontinuation

1. Pharmaceutical development :

In the pharmaceutical development phase, the objective is to design the products and plan the steps for the manufacturing process. The company must focus on maintaining process continuity and meeting the needs of patients, healthcare professionals, regulatory authorities and internal customers.

The technical activities conducted in this phase are:

- Developing drug substances
- Developing formulations that include both container and closure systems
- Developing analytic methods

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

- Developing manufacturing processes and plans for the scale-up
- Manufacture of investigational products

ICH Q10 applies to the manufacturing and manufacture of all pharmaceutical products. This also applies to medicinal products that are still in the development stage and have not been approved for the market, they are called investigational products.

2. Technology transfer :

The purpose of the technology transfer process is to transfer knowledge about processes and products from development to production.

- This phase involves the following technical activities:

a)Transfer of products from development to manufacturing

b)For marketed products, transfer between manufacturing and testing sites

3. Commercial manufacturing :

The goal of the commercial manufacturing phase is to help pharmaceutical companies manufacture products through continuous improvement processes and under controlled conditions. A pharmaceutical quality, process performance, appropriate controls, identification and evaluation of improvement opportunities, and knowledge development.

The technical activities that companies must perform are:

- Acquire and control materials
- Provide facilities, equipment, and utilities
- Fabricate packaging materials and labels
- Store, release, or distribute the manufactured products
- Ensure quality control and assurance

4. Product discontinuation :

Product discontinuation activities aim to effectively manage the final stage of the product life cycle.

- At this stage, the following technical activities should be performed.

1. Document retention and sample retention management
2. Continuous product evaluation and reporting

Managing product life cycle stage objectives creates a lot of documentation that needs to be properly maintained to ensure compliance with ICH Q10.

Elements:

A)Process performance & product monitoring system:

Monitor process performance and product quality System (PPPQMS) An effective PQS must include improvements A PPPQMS that proactively ensures processes and Production remains under control and is continuous Modified as appropriate, to provide increased assurance of product quality and process efficiency. Quality product reviews should include a summary Evaluation of process performance and product quality. Even the ICH identifies high-level principles for Q10. Monitoring programs can provide additional details Increased insight to determine the effectiveness of program An enhanced PPPQMS may include:

1. Tools for measuring the process and the method of the method including process capability, ie statistical process controls.
2. Periodic evaluation with transdisciplinary subjects

Subject matter experts to monitor trends and/or deviation Integration of information from process and method performance and product complaints, audits/inspections, and pharmacovigilance programs.

3. Identification of necessary or desirable PACs for monitoring

Control the conditions, ensuring the availability of the product and Continuous improvement of products, processes, and control strategy.

4. Quality plan to identify, communicate and implement key quality objectives to drive continuity Improvement of PQS.
5. Raising significant issues or trends For management review and possible changes quality plan.
6. Enhanced monitoring and samples of product quality after major changes with instructions the pharmacovigilance program.

B) Corrective and Preventive Action(CAPA):

Design and use of the CAPA section of the PQS As a result, product and process improvement is required. An effective CAPA system monitors and manages the unanticipated risks and consequences of PACs and allows appropriate actions to be taken to correct them. Prevent problems and their recurrence. CAPA system:It also provides insight into how PQS can be improved. Unexpected events such as complaint investigations may trigger corrective actions (CAs) Product rejection, misunderstanding, recall, deviation, Audits, regulatory audits, QRM and

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

Negative trends in process performance and production Quality control. Everyone is expected Key to deep investigation and root cause analysis is organized. Preventive actions (PA) can be carried out continuously improvement initiatives such as new products and processes knowledge is acquired. These are designed to predict and prevent PA problems, provide low deviation rates, and emphasize the need to learn from deviations, deviation trends and complaint/recall incidents. C) Change management system:

An effective change management system is essential for evaluating, approving and implementing changes. A team of experts with relevant knowledge and expertise will review the proposed changes to ensure their technical feasibility. After implementation, an evaluation should be conducted to ensure that the goals of the change have been achieved. Simpler QMS provides robust change control management capabilities that enable companies to effectively plan, document and manage all changes.Using our software, companies can benefit from automatic reminders and notifications that inform employees about change requests and related activities.

C) Management review of process performance and product quality:

Management reviews should ensure that process performance and product quality are managed effectively throughout the life cycle. Depending on the size and complexity of the company, the evaluation process may vary in frequency and level of detail. Effective communication and escalation mechanisms should be incorporated to address quality issues and involve senior management in a thorough review.

A management review should include:

Review the results of regulatory inspections, audits and commitments to regulatory authorities.Customer satisfaction quality assessment, process and product monitoring findings and effectiveness of changes.

Evaluation of implemented control measures based on previous management reviews.

Relationship of ICH Q10 to regional GMP requirements ,ISO Standards& Q7:

Regional GMP requirements, ICH Q7 guidelines, "Good Manufacturing Practice Guide to Active Pharmaceutical Ingredients" and ISO Quality Management System The guidelines form the basis for ICH Q10. To achieve the objectives listed below.

ICH Q10 defines certain quality system elements and extends GMPs Management responsibilities. ICH Q10 provides an integrated model of a pharmaceutical quality system is in place and is intended throughout the product life cycle.

It can be used in conjunction with regional GMP requirements.Regional GMPs do not clearly address all stages of a product's life cycle (eg: development). Quality system components and management responsibilities The guidelines described in this guide are intended to promote science and risk-based use.An approach at each stage of the life cycle that leads to continuous improvement The entire product life cycle.

Enablers :

1. Knowledge management:

ICH Q10 defines KM as "a systematic approach to acquiring, analyzing, storing and disseminating information. In relation to products, manufacturing processes and ingredients. In practice, KM integrates the existing and the new obtained information to inform risk management and Guide PAC decisions. Examples include knowledge PPPQM, Deviations, Trends, Complaints,Recalls, product quality reviews and management reviews.Developmental studies with design of experiments, It should also be considered to acquire new knowledge, that is in addition, enhanced data analysis and analysis, statistical and mathematical tools and Predictive models. Extended access and use of Technical and operational information, combined with Increased staff capacity based on the latest product and process knowledge, enabling faster implementation new knowledge for continuous quality improvement and the availability of the product in the commercial phase.To enable effective PAC management, KM should be used as part of PQS. KM must incorporate both Clear and concise knowledge aimed at better understanding the risks and benefits of a given PAC. For example, Product and process knowledge should serve as input Towards a control strategy to better understand the relationship Between parameters and attributes. can have the same input it can be used during the risk management of PAC. The components of KM must be defined in PQS and is maintained by appropriate mechanisms to activate Quick access to product and process knowledge. Method The acquisition and dissemination of information must be systematic and standardized. To be taken by management Active roles in the promotion and use

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

of KM, defining roles, expectations and maintaining incentives System robustness and timely implementation new knowledge. Education intervention, then action Reviews ("lessons learned"), job shadowing, and active Expert networks are just a few examples of processes and tools which require active promotion to maintain their viability and benefit for PAC management. As described in ICH Q10 KM as an enabler of PQS, a review of new knowledge should occur in the context of identifying candidates for When reviewing PACs and change requests.

2. Quality risk management:

An effective QRM should provide a patient-centered decision-making framework to ensure that it is systematic and Risk-based and data-driven decision making Used for all PACs. This includes related decisions Depending on whether the PAC continues or not Correct risk-benefit balance, how to manage risk Depending on the level of risk, it may be introduced by the PAC and a regulatory compliance strategy for the PAC. PQS elements and enablers must jointly identify risks to the product's availability, regulatory status, or continued demand. It is important to show the improvement product and understanding the process for identifying risk levels And manage the control strategy accordingly. QRM should help identify changes that reduce risk. Product and process failures and problems and improvements Performance of the process. Ensure effective QRM That the product does not introduce any unacceptable risks Quality and patient safety due to PAC. At the very least PACs should not increase risk beyond that Current level. Risk assessment based on current product and process knowledge, control strategy and product life They should be cycled for identified PACs. Of A PAC risk assessment should assess capacity. For all related products, processes, risks and benefits and systems that may be affected by this change. Certain PACs may be classified differently based on level of expertise, risk management, and PQS. Effectiveness risk assessment results Change planning, prioritization, implementation and scheduling must be managed. The rigor of the risk assessment associated with the PAC should be proportionate. including the complexity and severity of the change. Residual risk or any unintended consequences Changes (during and after change implementation) Affected products, processes, and systems must be evaluated to ensure they are operating at acceptable standards. As appropriate, residual risk and The effectiveness of the change should be monitored. After implementation to ensure that there is control It is sitting A process mechanism should be established for capture. Control and monitor key risks to product quality, effective for applied and pending PACs and secure.

CFR-21 PART-11

Introduction :

Organizations involved in the manufacturing of pharmaceuticals and other products critical to human health have a primary responsibility to assure compliance against regulations, governing all aspects starting from purchase of raw materials to release of finished products including data management, adherence to approved methods for testing product quality, quality assurance including documentation, etc., Data integrity in the analytical and life science laboratory is the cornerstone for compliance and rests on strong procedural, behavioural and technical controls.

While data integrity was already recognized in the late 1980s, focus in the mid 1990s shifted to the use of electronic signatures leading to the US FDA promulgating US 21CFR Part 11, Electronic Records, Electronic Signatures. If we think and plan to work with the prospects of Quality by Design (QbD), 21CFR shall be considered as a mandatory part of URS by customers while designing and ordering analytical equipment. While discussing 21 CFR, some question always arises in our minds, like:

- Does it govern only compliance part, or it also adds to the profit of the drug maker in long run?
- Interpretation as a cost generating project with regards to its implementation and sustenance is justified?
- Why reluctance for implementation until enforced, despite systematic compliance? For more understanding, let us go through some definitions first, as an introduction to the 21 CFR Part 11 with regards to its origin and journey that was started from August 20, 1997.

CFR:(Code Of Federal Regulations)

- The Code of Federal Regulations (CFR) is the codification of the general and permanent rules and regulations (sometimes called administrative law) published in the Federal Register by the executive departments and

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

agencies of the federal government of the United States.

- The CFR is divided into 50 titles .
- Each title is further divided into chapters, subchapters, parts, and sections.
- The online CFR is a joint project authorized by the publisher, the National Archives and Records Administration's (NARA) Office of the Federal Register (OFR), and the Government Publishing Office (GPO) to provide the public with enhanced access to Government information.
- Each volume of the CFR is updated once each calendar year and is issued on a quarterly basis.
- The soft-cover volumes of the CFR are issued each year :

1. Titles 1-16 are updated as of January 1
2. Titles 17-27 are updated as of April 1
3. Titles 29-41 are updated as of July 1
4. Titles 42-50 are updated as of October 1

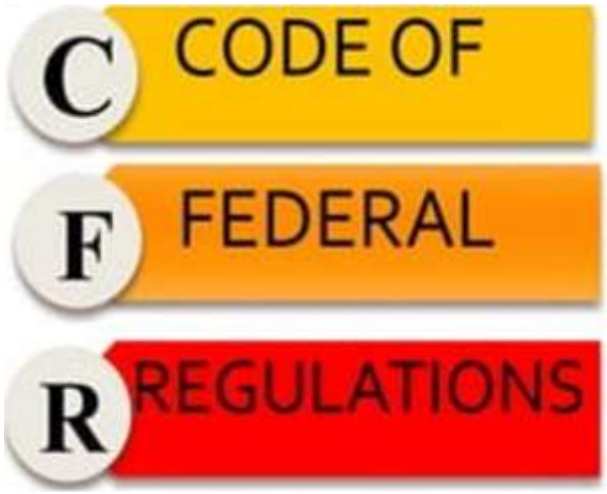

Fig 5 : CFR

History of CFR:

- The Federal Register Act - amended in 1937 to provide a "codification" of all regulations every five years - known as Code of Federal Regulations.
- The first edition of the CFR was published in 1938 and included all finalized regulations that were published in the Federal Register from March 14, 1936 to June 1, 1938
- Beginning in 1963 for some titles and for all titles in 1967, the Office of the Federal Register began publishing yearly revisions.
- Beginning in 1972 - published revisions were conducted in staggered quarters.

CFR Title 21:

- Title 21 CFR Part 11 is part of Title 21 of the Code of Federal Regulations that establish the United States Food and Drug Administration (FDA) regulations on electronic record and electronic signature (ERES).
- 21CFR Part 11 (Part 11) applies to electronic record and electronic signature that persons create, modify, maintain, archive, retrieve, or transmit under any record or signature requirement set forth in the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or any FDA regulation.
- Title 21 is the portion of the code of Federal Regulations that governs food and drug within the United States

Chapter I: Food and Drug Administration (FDA)
Chapter II: Drug Enforcement Administration (DEA)
Chapter III: Office of National Drug Control Policy (ONDCP).

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

Fig 6 : Titles

Whatis 21 CFR PART 11?

- 21 CFR Part 11 is the FDA's regulations for electronic records and electronic signatures.
- It outlines the administration of electronic records in a medical device company's quality management system.
- Since 21 CFR Part 11 was first published in 1997, our electronic systems and their capabilities have advanced enormously
- 21CFR11 is a law that ensures that companies and organizations implement good business practices by defining the criteria under which electronic records and signatures are considered to be accurate, authentic, trustworthy, reliable, confidential, and equivalent to paper records and handwritten signatures on paper.
- Part 11 essentially allows any paper records to be replaced by an electronic record, and allows any handwritten signature to be replaced by an electronic one.

In other words, it applies to record in electronic form that are created, modified, maintained, archived, retrieved, transmitted under any record requirements set forth in Agency regulations and submitted to the Agency under the Federal Food, Drug and Cosmetic Act and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in the Agency Regulations

Fig 7 : 21 CFR Part 11

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

What is the key purpose 21CFR?

- It is the FDA's regulations for electronic documentation and electronic signatures.
- It outlines the administration of electronic records in quality management system

PART 11 Electronic Records ; Electronic Signatures :

It is divided into 3 subpart they are as follows:

- **Subpart A General Provisions**

11.1 Scope.
11.2 Implementation.
11.3 Definitions

- **Subpart B Electronic Records**

11.10 Controls for closed systems.
11.30 Controls for open systems.
11.50 Signature manifestations.
11.70 Signature/record linking.

- **Subpart C Electronic Signatures**

11.100 General requirements.
11.200 Electronic signature components and controls.
11.300 Controls for identification codes/passwords.

Subpart A-General Provision :

11.1 Scope:

- The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.
- This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.
- Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.
- Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with § 11.2, unless paper records are specifically required.
- Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.
- This part does not apply to records required to be established or maintained by 1.326 through 1.368 of this chapter. Records that satisfy the requirements of part 1, subpart J of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.
- This part does not apply to electronic signatures obtained under of this chapter.

This part does not apply to records required to be established or maintained by part 117 of this chapter. Records that satisfy the requirements of part 117 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

- This part does not apply to records required to be established or maintained by part 507 of this chapter. Records that satisfy the requirements of part 507 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.
- This part does not apply to records required to be established or maintained by part 112 of this chapter. Records that satisfy the requirements of part 112 of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part

11.2 Implementation:

- People can use electronic records instead of paper ones for records they need to maintain but don't need to submit to the agency. They can also use electronic signatures instead of traditional ones, as long as they meet the requirements.
- For records submitted to the agency, electronic records and signatures are allowed if they meet the requirements and are specified in the public docket. The docket will detail which documents can be submitted electronically and to which agency receiving unit. If not specified, paper records must

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

accompany electronic submissions, and individuals should check with the intended receiving unit for details on how to proceed.

11.3 Definitions:
- Act: Federal Food, Drug, and Cosmetic Act.
- Agency: Food and Drug Administration.
- Biometrics: Verifying identity based on unique physical features or actions.
- Closed system: System access controlled by those responsible for electronic records.
- Digital signature: Electronic signature using cryptographic methods for authentication.
- Electronic record: Digital representation of text, graphics, data, etc., created, modified, or maintained by a computer system.
- Electronic signature: Legally binding computer data compilation authorized by an individual.
- Handwritten signature: Scripted name or mark executed by an individual for authentication.
- Open system: System access not controlled by those responsible for electronic records.

Subpart B—Electronic Records:
11.10 Controls for closed systems:
- Procedures and controls for closed systems to ensure authenticity, integrity, and confidentiality of electronic records.
- Includes validation of systems, protection of records, limiting system access, audit trails, operational and authority checks, and ensuring personnel have the necessary education and training.
- Written policies for accountability and to deter falsification of records and signatures.

11.30 Controls for open systems:
- Similar procedures and controls as closed systems, including document encryption and digital signature standards for authenticity, integrity, and confidentiality.

11.50 Signature manifestations:
- Signed electronic records must include the printed name of the signer, date, time, and meaning associated with the signature.
- Subject to the same controls as electronic records.

11.70 Signature/record linking:
- Electronic and handwritten signatures must be linked to respective electronic records to prevent falsification.

Subpart C—Electronic Signatures:
11.100 General requirements:
- Each electronic signature must be unique and not reused by others.
- Organization must verify the individual's identity before sanctioning their electronic signature.
- Persons using electronic signatures must certify to the agency that they are equivalent to traditional handwritten signatures.

11.200 Electronic signature components and controls:
- Electronic signatures not based on biometrics must use at least two identification components.
- Collaboration of two or more individuals required for attempted use by anyone other than the genuine owner.
- Electronic signatures based on biometrics designed to ensure use only by genuine owners.

11.300 Controls for identification codes/passwords :

- Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.
- Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).
- Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.
- Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

WHO-GMP Requirements :

GMP, or Good Manufacturing Practice, is a set of rules created by regulatory agencies to make sure products like medicines, food, and cosmetics are consistently made and controlled according to quality standards. Here are some important points about GMP:

1. Quality Control:
- GMP requires companies to have a Quality Control Unit (QCU) to oversee and implement quality control measures.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

- It involves testing raw materials, ongoing samples, and final products to make sure they meet quality standards.
- Specifications are set for different attributes like appearance, strength, and purity that products must meet.
- Stability testing is done to check how products hold up under different conditions.
- Analytical methods used for testing must be reliable and accurate.
- Records of all these activities must be kept for inspection.

2. Facilities and Equipment:

- GMP rules say manufacturing places and equipment must be designed and maintained to prevent contamination.
- The layout should be organized to avoid mix-ups and contamination.
- Environmental controls like temperature and cleanliness are crucial.
- Regular cleaning and maintenance of equipment are required.
- Equipment must be validated to make sure it works correctly.

3. Personnel Training and Hygiene:

- Workers must be trained on GMP rules, safety, and quality control.
- They should wear proper protective clothing and follow good hygiene practices.
- Hand hygiene is crucial to prevent contamination.
- Personal habits like not eating or drinking in work areas are important.
- Workspaces should be kept clean, and spills must be cleaned up promptly.

4. Documentation and Record-Keeping:

- GMP requires detailed records for everything – from procedures to testing results.
- Document control procedures are set up to make sure all important documents are handled properly.
- Standard Operating Procedures (SOPs) guide employees on how to carry out tasks.
- Batch records document the entire production history of a product.
- Changes to processes or documents must be controlled and documented.
- Records are kept for a certain period and stored securely.

5. Validation and Qualification:

- Validation is about proving that manufacturing processes consistently make high-quality products.
- Process validation involves understanding, demonstrating, and continuously verifying the manufacturing process.
- Analytical method validation ensures testing methods are reliable.
- Equipment used in manufacturing processes needs to be validated.
- Records of all validation activities are important for showing that everything is done correctly.

These GMP requirements ensure that products are made and controlled properly, meeting the necessary quality standards. accurate, reliable, and suitable for their intended purpose. It involves demonstrating method specificity, linearity, accuracy, precision, and robustness

- **Cleaning Validation:**

Cleaning validation verifies that cleaning procedures effectively remove residues from equipment surfaces to prevent contamination of subsequent products. It involves establishing acceptance criteria, selecting worst-case scenarios, performing cleaning studies, and documenting results.

- **Equipment Qualification:**

Installation Qualification (IQ): IQ verifies that equipment is properly installed and meets manufacturer specifications, regulatory requirements, and design criteria. It involves documenting equipment installation, verifying utilities connections, and ensuring proper placement.

- **Operational Qualification (OQ):**

OQ ensures that equipment operates according to predefined specifications and performance requirements. It involves testing equipment under normal operating conditions, assessing functionality, and documenting results.

- **Performance Qualification (PQ):**

PQ demonstrates that equipment consistently performs as intended in a simulated or actual production environment. It involves conducting tests using actual production materials, operating parameters, and environmental conditions.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

- **Facility Design Qualification (FDQ):**

FDQ verifies that facility design and construction meet regulatory requirements, GMP guidelines, and industry standards. It involves evaluating architectural drawings, engineering specifications, and construction documentation.

- **Facility Commissioning:**

Facility commissioning ensures that systems and utilities (e.g., HVAC, water, utilities) function as intended and meet operational requirements. It involves testing, adjusting, and documenting system performance to ensure reliability and compliance.

- **Computer Systems Validation (CSV):**

CSV ensures the integrity, reliability, and security of computerized systems used in GMP-regulated activities. It involves validating hardware, software, and associated processes to ensure data accuracy, completeness, and traceability.

- **Documentation and Reporting:**

Validation and qualification activities require thorough documentation of protocols, procedures, test results, deviations, and conclusions.

Documentation should be comprehensive, well-organized, and maintained in accordance with GMP requirements.

Final validation and qualification reports summarize study objectives, methodologies, results, conclusions, and recommendations for regulatory submission and internal reference.

6.Complaint Handling and Product Recall:

GMP regulations require manufacturers to have procedures in place for handling customer complaints, investigating product quality issues, and implementing product recalls if necessary to protect public health and safety.

Complaint handling and product recall requirements are critical aspects of Good Manufacturing Practice (GMP) aimed at ensuring the safety, efficacy, and quality of products manufactured in regulated industries. Here's an overview of complaints handling and recall requirements under GMP:

- **Complaint Handling:**

Definition of Complaint: A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product.

- **Complaint Handling Procedures:**

GMP requires manufacturers to establish written procedures for receiving, documenting, investigating, and resolving complaints in a timely and effective manner.

- **Complaint Evaluation:**

Upon receipt of a complaint, manufacturers should promptly evaluate the nature and severity of the complaint, determine whether it represents a potential quality issue or safety concern, and initiate an investigation as appropriate.

- **Investigation and Root Cause Analysis:**

Complaint investigations should be thorough and systematic, involving root cause analysis to identify the underlying reasons for the complaint and potential corrective actions to prevent recurrence.

- **Documentation and Record-Keeping:**

All complaint-related activities, including receipt, investigation, resolution, and follow-up actions, should be documented in detail. Complaint files should include complaint forms, investigation reports, correspondence, and any corrective or preventive actions taken.

- **Trend Analysis:**

Manufacturers should periodically review complaint data to identify trends, patterns, or recurring issues that may indicate systemic problems with product quality, design, manufacturing processes, or supplier performance.

- **Product Recall:**

- **Definition of Recall:**

A product recall is the voluntary or mandatory removal or correction of a product from the market when it is determined that the product poses a risk to public health, safety, or welfare, or fails to meet regulatory standards or specifications.

- **Recall Procedures:**

GMP requires manufacturers to establish written procedures for initiating, implementing, and documenting product recalls. Recall procedures should addressnotification to regulatory authorities, customers, distributors, and other relevant stakeholders.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

- **Recall Classification:**

Recalls are typically classified based on the severity and potential impact of the product defect or hazard. Common recall classifications include:
Class I: Products with a high risk of serious adverse health consequences or death.
Class II: Products with a moderate risk of adverse health consequences.
Class III: Products with a low risk of adverse health consequences.

- **Recall Strategy and Communication:**

Manufacturers should develop a recall strategy that outlines the scope of the recall, communication plan, recall notification process, retrieval and disposition of recalled products, and public notification procedures.

- **Recall Effectiveness Checks:**

Manufacturers should conduct effectiveness checks to ensure that the recall has been carried out successfully, and all affected products have been removed from the market or corrected as appropriate.

- **Documentation and Reporting:**

All recall-related activities, including initiation, implementation, effectiveness checks, and communication with regulatory authorities, should be documented and reported in accordance with regulatory requirements.

7.Audits and Inspections:

Regulatory agencies conduct regular inspections and audits of manufacturing facilities to ensure compliance with GMP requirements. Manufacturers must cooperate with inspections, provide access to facilities and records, and address any deficiencies identified during inspections.

Overall, GMP requirements are essential for ensuring the quality, safety, and efficacy of products manufactured for human and animal use. Compliance with GMP regulations is mandatory for manufacturers in the pharmaceutical, food, and healthcare industries to ensure consumer protection and public health.

Principles of Six Sigma
Introduction :

In order to cope with modern societies they are actively trying to improve their overall performance Increasing intensity of competition. In this task, modern organizations strive for relevance Policies in all their endeavours. One of the characters Strategies are widely and profoundly used in modern societies Continuous Quality Improvement.

Bill's efforts led to the development of Six Sigma as we know it today at Motorola Smith, a reliability engineer, in the 1980s. A true confusionThe work of Jack Welch, the then CEO of Six Sigma, popularized Six Sigma In 1995 General Electric. Welch had noted the success achieved through BillSmith method and pioneered the Six Sigma method at GE. The term "Six Sigma" refers to the statistical measurement of defect rates in a process.With accounting mechanisms dependent on it, it exhibits a systematic and systematic process 3.4 A process improvement approach aimed at low defect levels. One chance in a million, or Six Sigma. To help explainThe significance of six sigma defect rates in systems, for someUseful examples of 99 per cent quality and high quantity variation Six Sigma Quality in Different Contexts. The concept of Six Sigma makes 'zero defect production' virtually and easy to achieve Get the most out of it. To achieve this goal, two strategies are followed. There is one That, damage prevention activities must be carried out within the organization By using the Define, Measure, Analyze, Improve and Control (DMAIC) components. And define, measure, analyze, design and verify (DMADV) components.

Background of Six Sigma :

Today, Six Sigma (6σ), a set of techniques and tools used to improve productivity, stands out A history of the further development of the organizational system and its broad set of tools and methods.Sigma Belts – those trained in some or all aspects of Six Sigma – are strongly encouraged. Organizations looking for individuals to further build their careers. As Bru said (2015), the development of Six Sigma can be attributed to Carl Friedrich Gauss (1777-1855), who is considered Among the most influential mathematicians in history. Gauss developed the concept of a general curve, or Normal distribution, also known as Gaussian distribution or Gaussian curve. An important basis for The mathematical concept used in Six Sigma is the German mathematician Friedrich Gauss Distribution curve (also called clock curve). There are exceptional effects of normal dispersion Standard deviation, indicated by the Greek letter designated 'σ' ('sigma'), away from the mean. You whom you trust For practical quality control, processes and products are

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

measured and evaluated and discrepancies are detected The parallel directions and propagation patterns indicate variability.

Initially, the Six Sigma methodology, which is commonly used in the retail industry, is often considered As the last edition of Total Quality Management (TQM) and fast forward to 1985, Six Sigma started at Motorola. The evolution of Six Sigma began in 1985Memo from then-Motorola quality engineer Bill Smith to then-Motorola CEO Bob Galvin. Memo, Smith reported, and there is a statistically significant relationship between core life and recycling rates During the production process. In 1986, Bill Smith, a senior engineer and internal analyst Motorola's communications department came up with the concept of Six Sigma in response to widespread complaints Field deals force about licensing issues. This is an alternative to adaptationMeasured imperfection, Six Sigma is close to perfection. Smith took the first measurements And equations that are the beginning of Motorola's Six Sigma philosophy. They followed his plansPresident Bob Galvin, whom Smith marveled at and understood the process. The key toaddressing quality concerns. Six Sigma has become integral to Motorola's product delivery process Which is good for consumer use.

Definition of six Sigma :
Six Sigma is a methodology of continuous improvement in customer satisfaction and profitability. Which is used to improve effectiveness and efficiency.

Methodologies used in six Sigma :
There are 2 main methodologies used in six Sigma such as
1) DMAIC
2) DMADV

1) DMAIC :
It refers to a data-driven approach to process improvement. This approach is used to improve existing business processes.

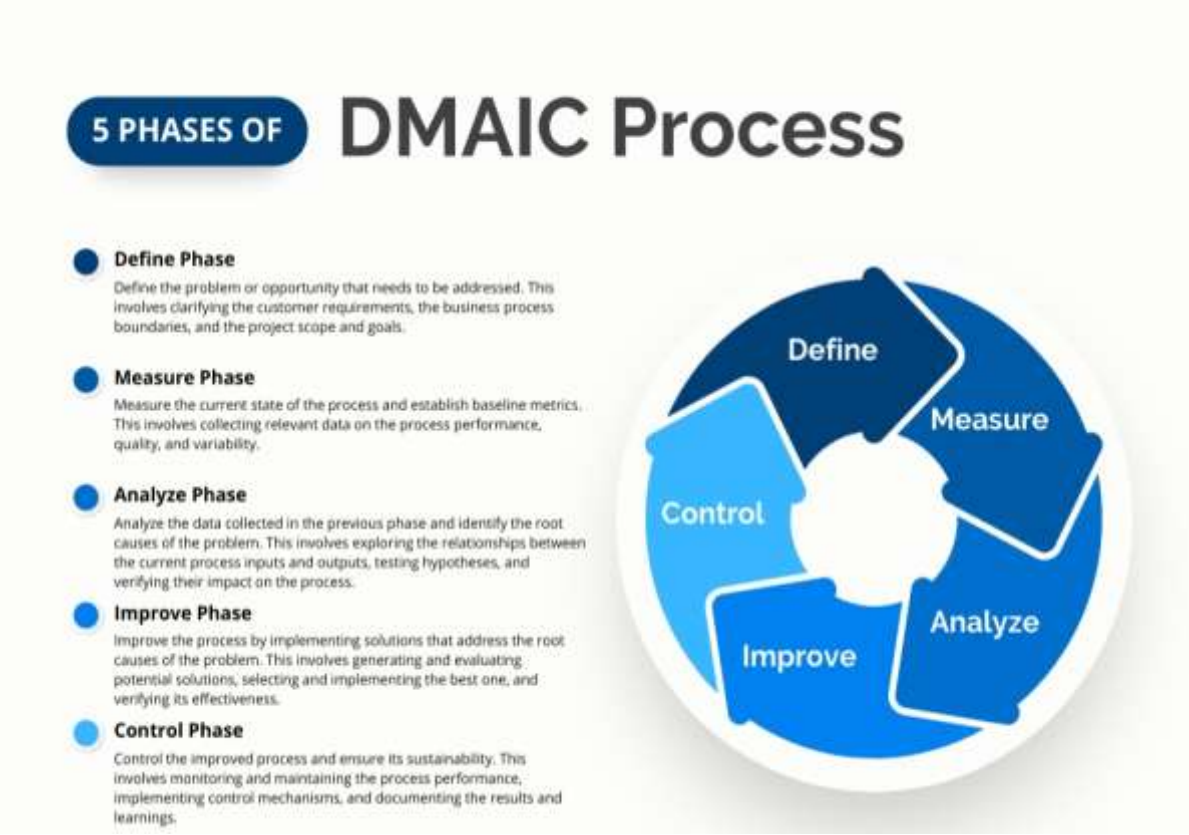

Fig 8 : DMAIC Process

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

2) DMADV : It refers to a data-driven approach to the design of products and services. This approach is used to develop or process new product designs in a way that results in a more predictable, mature and error-free workflow.

Fig 9 : DMADV Process

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

- **Implementation of six Sigma :**

In order to implement Six Sigma in an organization, the first step is to make the case effectively for accounting tools such as Six Sigma and get stakeholder buy-in for the potential benefits. Additionally, it's important to set the expectation that complete blamelessness isn't realistic. However, there are some best practices that can help ensure as much progress as possible. Once managementunderstands the potential behind Six Sigma, the following nine steps can help implement a Sigma project and ensure a clean release.

Step 1: Motivate stakeholders by pointing out loss of quality.

Step 2: Conduct project management and obtain necessary resources.

Step 3: Educate team members about Six Sigma management techniques.

Step 4: Create a quality control diagram and identify priorities.

Step 5: Assign ownership to all involved team members.

Step 6: Make sure the right metrics and indicators are measured.

Step 7: Analyze the cause to understand the error.

Step 8: Manage the process to ensure proper execution and continuous improvement.

- **Principles of Six Sigma :**

Fig 10 : Principles of Six sigma

1) Customer Focused :

The ultimate goal is to maximize profits for customers. Thus, businesses need to understand the needs of their customers and suppliers. This involves setting quality standards as desired by the market or customers.

2) Identify Root causes :

Outline steps to identify unwanted areas and collect relevant data. State the objectives of data collection, the purpose of data collection and the desired implications. If additional data needs to be collected, or if the data needs to be cleaned up, determine if the data is helping to achieve the objectives. Find the problem and the cause.

3) Eliminate Defects :

After identifying the problem, make appropriate system changes to eliminate the defect. Eliminate any activity within a system that does not contribute to customer value. If the value chain cannot reveal problem areas, various tools are used to identify problem areas and processes. Removing externalities and defects removes constraints from a system.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 102-122 www.ijprajournal.com ISSN: 2249-7781

4) Involve stakeholders :

A systematic approach should be followed where all stakeholders collaborate and contribute to finding solutions to complex problems. The team must be proficient in the methods and principles used. Thus, specialized knowledge and training are needed to reduce the risks of project failure and ensure maximum project performance.

5) Flexible System :

Whenever an ineffective or faulty system is removed, employee attitudes and work habits must change. An environment that is flexible and responsive to system changes can lead to efficient operations.The agencies involved must be able to adapt easily to changes. Companies that periodically review data and make appropriate changes to their processes can gain a competitive advantage.

II. CONCLUSION :

In conclusion, a well-implemented pharmaceutical quality management system is pivotal in ensuring the integrity, safety, and efficacy of pharmaceutical products. It serves as the cornerstone for compliance with regulatory standards and fosters a culture of continuous improvement within the industry. As technology advances, embracing innovative solutions becomes crucial, facilitating more efficient and effective quality processes.

The emphasis on risk-based approaches underscores the industry's commitment to proactively addressing potential challenges. Moreover, fostering a robust quality culture throughout the organization promotes accountability and a shared responsibility for delivering high-quality pharmaceuticals.

Looking ahead, the pharmaceutical landscape is dynamic, and adapting quality management systems to evolving regulations and technological advancements is imperative. Collaboration between industry stakeholders, regulatory authorities, and healthcare professionals remains essential for maintaining and elevating the overall quality standards, ultimately safeguarding patient well-being. In essence, a resilient pharmaceutical quality management system is not merely a regulatory requirement but a commitment to excellence and patient-centric care.

REFERENCES :

[1]. B. Mazumder, S. Bhattacharya, A. Yadav, “Total quality management in pharmaceuticals: a review”, Total Quality Management.Vol-3, 365-375.

[2]. J. N. Morfaw,2009."Total quality management (TQM) A model for the sustainability of projects and programs in Africa" University press of America,Vol-1, 8-9

[3]. Sanjay L. Ahire, Robert Landeros , Damodar Y. Golhar, “Total Quality Management: A Literature Reviewandan Agendaforfutureresearch”, Production and operation management, vol-4, issue 3

[4]. Ahire, S. L., Golhar, D. Y. & Waller, M. A. (1996). “Development and validation of TQM implementation constructs”. Decision Sciences, 27 (1), 23–56.

[5]. Black, S. A. & Porter, L. J. (1996). “Identification of the critical factors of TQM”. Decision Sciences, 27 (1), 1–21.

[6]. Clinton, R. J., Williamson, S. & Bethke, A. L. (1994). “Implementing total quality management: the role of human resource management”. SAM Advanced Management Journal, Spring, 10–16.

[7]. Hackman, J. R. & Wageman, R. (1995). “Total quality management: empirical, conceptual and practical issues”. Administrative Science Quarterly, 40, 309–342.

[8]. J. M. Juran & A. B. Godfrey (Eds) (1999). Juran's Quality Control Handbook, 5th Edn. New York: McGraw-Hill.

[9]. Kochan, T. A., Gittell, J. H. & Lautsch, B. A. (1995). “Total quality management and human resource systems: an international comparison”. International Journal of Human Resource Management, 6 (2), 201–223.

[10]. Thomas C. Powell, “Total quality management as competitive advantage: A review and empirical study”, Strategic Management Journal, vol-16 issue 1

[11]. Josh Tari. J, (2005), "Components of successful total quality management", The TQM Magazine, Vol. 17 No. 2, pp. 182-194.

[12]. Martine J. Lipa, Anne Greene, Nuala Calnan, "Knowledge Management as a Pharmaceutical Quality System Enabler: How Enhanced Knowledge Transfer Can Help Close the ICH Q10 to ICH Q12 Gap",PDA Journal of Pharmaceutical Science and Technology January 2021, 75 (1) 64-90.
[13]. Sean A. VanDuyse, Micheal J. Fulford, Micheal G. Bartlett, "ICH Q10 Pharmaceutical Quality System Guidance : Understanding its impact on pharmaceutical quality", The AAPS Journal, 2021 vol-23.
[14]. Ljuba Karanakov, Jasmina Tonic-Ribarska , Marija Glavas-Dodov , Suzana Trajkovic-Jolevska, "Analysis and critical review of ICH Q8, Q9 and Q10 from a generic pharmaceutical industry view point", Macedonian pharmaceutical bulletin, 57 (1, 2) 85 - 96 (2011)
[15]. Carsten Aaberg, Heribert Dahmen, Cledwyn Davies, Pia Lise Sandau, Raman Srinivasa, "ISO 9001:2015 Verses ICH Q10 – A Comparison", PDA Journal of Pharmaceutical Science and Technology March 2021, 75 (2) 188-206.
[16]. Lipa, Marty; O'Donnell, Kevin; and Greene, Anne (2020) "Managing Knowledge and Risk : a Literature Review on the Interdependency of QRM and KM as ICH Q10 Enablers," Level 3: Vol. 15: Issue . 2, Article 3.
[17]. Richa Shukla, Gurmeet Singh Chhabra, "The Importance of Quality Management System in Pharmaceutical Industry", International Journal of Engineering Applied Sciences and Technology, 2023, Vol. 8 , Issue 07.
[18]. Nuala Calnan, Kevin O'Donnell and Anne Greene, "Enabling ICH Q10 Implementation- Part 1. Striving for excellence by embracing ICH Q8 and ICH Q9", PDA Journal of Pharmaceutical Science and Technology, November 2013, 67(6) 581-600.
[19]. ICH Q10, Pharmaceutical Quality System, June 2008.
[20]. Swartz, Micheal and Ira Krull, "21 CFR Part 11 and risk assessment: adapting fundamental methodologies to a current rule", LC-GC North America, vol-25 no. 1, 2007.
[21]. Indumathy Jagadeeswaran, Nandhini Palani, Ganesh Lakshmanan, "FDA-CFR Title 21- food and drugs: parts 800to 1299", Medical Devices Guidelines and Regulations Handbook, Chapter, 2022.
[22]. John Avellanet, "FDA 21 CFR Part 11 Revisited", Bioprocess International, 2009.
[23]. Victoria Lander, "21 CFR Part 11 and Risk Assessment: Adapting Fundamental Methodologies to a Current Rule", Pharmaceutical Technology Europe, vol-16, Issue-5, 2004.
[24]. Lopez, Orlando, "A Historical View of 21 CFR Part 211.68", Journal of GXP Compliance, vol-15, Issue-2, 2011.
[25]. George G. Kuniholm, "Steering a course for risk assessment: The impact of new draft guidance, 21 CFR Part 11 scope and application on the electronic records electronic signatures rule", The Quality assurance Journal, vol-7, Issue-9, 2003.
[26]. Micheal P, Owings, Paul A. Bleicher, "CFR 21 Part 11", Wiley Encyclopedia of Clinical Trials, 2008.
[27]. Richard M. Siconolfi, "A Journey along the 21 CFR Part 11 Life Cycle", The Quality Assurance Journal, vol-7, Issue-9, 2005.
[28]. R. D. McDowall, "Exploiting the Benefits of 21 CFR 11", American Pharmaceutical Review, 2000.
[29]. Eric G. Begun, "The Legal Risks of Compliance with the Electronic Signatures and Records Requirements of 21 CFR Part 11", American Pharmaceutical Reviews.
[30]. Tammala D. Woodrum, "21 CFR Part 11: The Role of Predicate Regulations and Associated Internal Policies", Sage Journals, vol-37, Issue-2, 2003.
[31]. K.T. Patel, N.P. Chotai, "Documentation And Records: HarmonizedGMP Requirements", Journal of Young Pharmacist, vol-3, Issue 2, 2011.
[32]. Patel K.T, Chotai. N. P, "Pharmaceutical GMP: Past, Present and A future- a review", An International Journal of Pharmaceutical Science , vol-63, Issue 4, 2008.
[33]. PetrellliFabio, Caraffa Alessandro, Scuri Stefania, Grappasonni Iolanda, Magrini Elena, Cocchini Aldo, "The requirements for manufacturing highly active or sensitising drugs comparing Good Manufacturing Practices", Acta Biomed, vol-90(2), 2019.

[34]. Julie Milstien, Alejandro Costa, Suresh Jadhav, Rajeev Dhere, "Reaching international GMP standards for vaccine production: challenges for developing countries", Experts Review of Vaccines, vol-8, Issue 5, 2009.
[35]. Gillian Chaloner, Roger Anderson, Anik Egan, "A WHO guide to good manufacturing practice requirements", World Health Organization, Geneva,1997.
[36]. Laurent Bretaudeau, Karine Tremblais, Francoise Aubrit, Marc Meichenin, Isabelle Arnaud, "Good Manufacturing Practice (GMP) Compliance for Phage Therapy Medicinal Products", Mini Review Articles, Antimicrobials, Resistance And Chemotherapy, vol-11, 2020.
[37]. Jayant Kumar, Ajmera Ramkishan, Madhugiri Prakash Venkatesh, "Bridging the Gap: Aligning GMP Requirements for Generic Manufacturing across the US, EU, Japan", International Journal of Pharmaceutical Investigation, vol-13(3), 2023.
[38]. Mohamed Abou-El-Enein, Andy Romhild, Daniel Kaiser, Corola Beier, Gerhard Bauer, Hans Dieter Volk, "Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: a novel tailored model for optimizing performance and estimating costs", Cytotherapy, vol-15, Issue 3, 2013.
[39]. Abubaker Abdellah, Mohamed Ibrahim Noordin, Wan Azman Wan Ismail, "Importance and globalization status of good manufacturing practice (GMP) requirements for pharmaceutical excipients", Saudi Pharmaceutical Journal, vol-23, Issue 1, 2015.
[40]. S. Lakshmana Prabhu, T.N.K. Suriyaprakash, K. Ruckmani, R. Thirumurugan, "Chapter 3- GMP in Pharma Manufacturing – Description of GMP as related to air handling units and prevention of contamination and implementation of GMP regulatory requirements", Developments in surface contamination and cleaning: types of contamination and contamination resources, vol-9, 2017.
[41]. Quality assurance of pharmaceuticals- A compendium of guidelines and related materials, Good manufacturing practices and inspection, World Health Organization, vol-2.
[42]. S.S. Khoja,P.H. Chauhan, F.S. Khoja, "A Review on Creation and handling of data in accordance with cGMP requirements in pharmaceuticals", Pharma Tutor, 2017.
[43]. Kalpesh T. Patel, Narendra P. Chotai, "Material Management for active pharmaceutical ingredients-Comprehensive GMP requirement and approach for compliance", An International Journal of Pharmaceutical Sciences, vol-3, Issue 2, 2012.
[44]. Ravi S. Reosekar, Sanjay D. Pohekar, "Six sigma methodology: a structured review", International Journal ofLean Six Sigma, vol-5, Issue 4, 2014.
[45]. E.V. Gijo, Johny Scaria, Jiju Antony, " Application of six sigma methodology to reduce defects of a grinding process", Quality and Reliability Engineering International, vol-27, Issue 8, 2011.
[46]. Yahia Zare Mehrjerdi, "Six sigma: Methodology, tools and its future", Assembly Automation, vol-31, Issue 1, 2011.
[47]. J. Antony, R. Banuelas Coronado, "Design for Six Sigma", Manufacturing Engineer, vol-81, Issue 1, 2022.
[48]. Lawrence O. Jenicke, Anil Kumar, Monica C. Holmes, "A framework for applying six sigma improvement methodology in an academic environment", The TQM Journal, vol-20, Issue 5, 2008.
[49]. Prabhakar Kaushik, Dinesh Khanduja, Kapil Mittal, Pawan Jaglan, "A case study: Application of six sigma methodology in a small and medium sized manufacturing enterprise", the TQM Journal, vol-24, Issue 1, 2012.
[50]. Ricardo Banuelas, Jiju Antony, Martin Brace, "An Application of Six Sigma to Reduce Waste", Quality and reliability engineering international, vol-27, Issue 8, 2005.