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Review on total quality management

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Abstract
With the introduction of total quality management, a new vista has opened for assured pharmaceutical quality. Quality of pharmaceuticals has always been a top concern for regulatory agencies around the world in order to facilitate production of medicines without batch to batch variations and maintain the same therapeutic effectiveness. Being a multifaceted strategy, total quality management essentially necessitates adherence to quality standards across the entire pharmaceutical production process. To put this idea into practice, it may be applied in various ways, including quality by design, quality risk management, and the six sigma approach, along with strict adherence to legal requirements. This article provides a concise overview of current overall quality management industrial practices with a focus on recent developments in online production monitoring, advanced analytical tools, and anti-counterfeiting technologies.

Keywords: Hair oil, herbs, formulation, preparation, evaluation, results and discussion

Introduction
In any industry, a product's quality is a crucial criterion because it directly affects the revenue generated by its sale. However, there is still another crucial justification for the need for high-quality products in the pharmaceutical sector. Since manufacturing mistakes can have harmful and even fatal consequences for the patients eating the products, this is one of the main reasons this business is so strictly controlled. As a result, it is essential that pharmaceutical items be produced in accordance with strict regulatory requirements.
The word "quality" is frequently used to describe how good or bad a product or service is. But defining this phrase is not so simple. Most frequently, it relates to how closely the product can fit the requirements and fulfil the customer's expectations. The degree to which a set of inherent characteristics satisfies the requirements is how ISO defines quality.
Although the term "quality" is frequently used and appears to be quite simple, it might be challenging to define accurately
It is described by ISO as "the extent to which a set of intrinsic qualities satisfies requirements." Degree describes the degree of satisfaction that a good or service provides. Therefore, a product may be described as outstanding, good, or bad quality based on the amount of pleasure. These characteristics, which are a part of the product and are in charge of ensuring satisfaction, are known as inherent characteristics. Customer needs, organizational needs, and the needs of other interested parties are all referred to as requirements.

- Another definition of quality is the non-inferiority or superiority of a thing.
- Since quality is a perception, various people may have different interpretations of it.

There are two categories of quality. meeting specifications
According to consumer comparisons with other products on the market, this is an excellent product.

Conformity level
It represents the degree to which a good or service was produced properly.
Quality is defined by the pharmaceutical business as adherence to the product's requirements. Depending on the product's medicinal efficacy, potency, etc., the requirements vary.

Quality Control
To ensure a high-quality product, multiple areas must be managed through quality management. Quality planning, Quality control, Quality assurance, and Quality improvement make up the four primary parts of quality management.

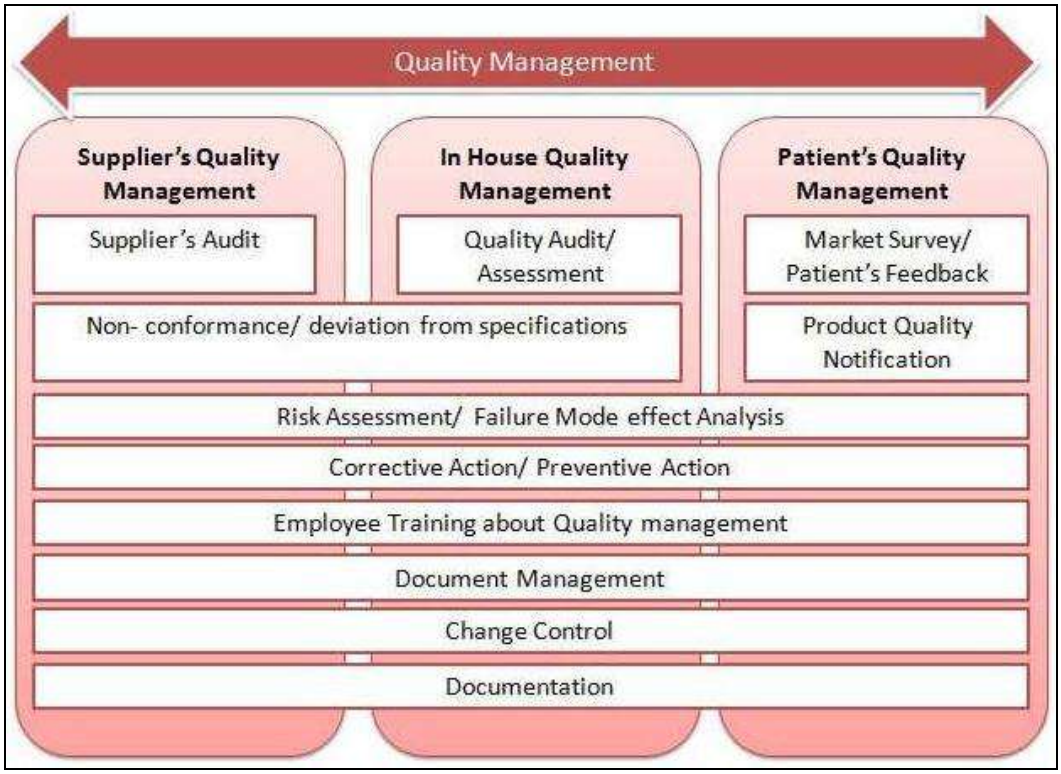


Fig 1: Shows a diagram of the quality management system.

The quality gurus have given several definitions of quality, including compliance to standards or specifications, usability, fulfilling customer expectations, and pleasing the customer. Although it is a word that is frequently used, quality can be relatively ill-defined. Quality is an extraordinarily elusive term that is both simple to visualize and challenging to define. It is a question of feeling, and each person will define it differently depending on their point of view.

The following are the eight qualities that must be present in order for an organization to succeed.

1. Performance: The main operational properties of the product.
2. Features: Additions to a product's fundamental qualities of operation.
3. Reliability: The likelihood that something won't break down over a certain time frame.
4. Conformance: How closely a product's operating characteristics and design adhere to predetermined criteria.
5. Product life is gauged by durability.
6. Serviceability: The quickness and simplicity of repair.
7. Aesthetics: A product's appearance, texture, flavor, and smell.
8. Quality as perceived by the buyer.

Quality Evaluation

Businesses were looking for strategies to cut down on the production of defective goods at the beginning of the 20th century. Frederick W. Taylor wrote a book titled "The Principles of Scientific Management" in 1911 that concentrated on the need for corporations to utilize people well. He suggested the idea of "clearly defined tasks" and "standard circumstances," as well as the assignment of individuals to the task of "inspection" of goods. This led to the birth of the "Inspection Department" and its focus was on preventing defects which in turn, developed into the concept of Quality Control.

Dr. W. Shewhart created techniques for statistical analysis of production processes during the 1930s. He demonstrated how variances in manufacturing procedures result in variations in product quality by using a "control chart." His statistical quality control theory focused on the identification and management of quality issues through the examination of several samples at various production stages. Japanese business executives aimed to improve the quality of their products, which were mainly seen as cheap knockoffs, in the 1940s. Western quality specialists including W. Edwards Deming, Joseph M. Juran, and Armand V. Feigenbaum visited Japan at their invitation to advise these businesses on their quality requirements.

Deming introduced statistical analysis and its application to quality control to the Japanese. Juran's lectures centered on the notion of involving managers in the quality process. Japanese businesses created "quality circles" in the early 1960s. These groups of workers met voluntarily to discuss how to improve a particular component of their work and then offered their ideas to management. Employee motivation to contribute at work increased as a result. The conversations gradually shifted from being solely about product quality to being about how the business as a whole could be improved. This is where the concept of "Total Quality" came from.

Feigenbaum delivered a paper at the inaugural global quality control conference in Tokyo in 1969. He introduced the phrase "Total Quality" in this passage. Ishikawa in Japan developed the idea of "Total Quality Control" at the same period, which was distinct from the western conception of total quality.

Industry leaders in the West started their own set of quality initiatives in the 1980s and 1990s after watching the significant advancements made by Japan in addressing quality challenges. The phrase "Total Quality Management," or "TQM," encompassed a wide range of

methods and tactics used to implement these objectives.

Introduction of TQM

The pharmaceutical industry, which deals with the production and marketing of pharmaceuticals, biological products, and medical devices used for the diagnosis and treatment of diseases as well as conducting research for the development of new products for human welfare, is a crucial component of our health care system. Since many pharmaceutical products are lifesaving, maintaining quality is crucial to preventing health risks. If products are of inadequate quality, they may have significant adverse effects or even cause the patient's or consumer's death. Regulatory authorities from many nations began implementing Total Quality Management after noticing flaws in traditional quality management systems (TQM). This TQM idea is crucial for maintaining and enhancing quality as well as for preventing faults. 1. At first, the idea of total quality control was employed, according to which quality was guaranteed solely on the basis of quality control parameters. However, this TQM approach focuses on enhancing quality in pharmaceutical products since it calls for thorough records, including records of batch manufacturing, validation, and standard operating procedures for each step. This evaluation provides details on quality, quality management, the state of the practice, and the demand for TQM. This article defines TQM as a comprehensive method for the quality management of pharmaceuticals by utilizing multiple quality management approaches such as excellent manufacturing practices, quality by design, quality risk management, etc., leading to high quality goods.

Procedures Prior To TQM

Final product quality control (FPQC), the only traditional quality management method used before to the development of TQM, was used to determine if the product obtained was of the intended quality or not. If all of the final product's parameters were found to be within acceptable limits, it was regarded as a high-quality product; however, if findings were found to be outside of acceptable limits, the product was deemed to be of low quality and was rejected. The primary flaw with conventional approaches was the absence of any procedures or processes for managing the quality of the final product. Only the quality control department was in charge of maintaining the product's quality; other departments were unconcerned, which frequently led to batch-to-batch variation.

TQM Evolution

Similar to conventional approaches, quality control testing only affects the final product. As the fault can only be discovered at the end of the process, they led to an increase in cost and time usage. The situation has altered as a result of the evolution and use of TQM, and now every department is concerned with product quality management. Every stage of the process is quality-checked, and if a problem does arise, it is only addressed at that precise moment. Quality is controlled at every stage and is not just dependent on final product quality control testing. So it also improved the product's quality and reduced the time and costs associated with batch failure or as a result of resolving a process-related issue. The pharmaceutical business should therefore apply TQM because it increases product quality, which is crucial because it is a key component of the healthcare system, and because it reduces production time, which eventually lowers product costs.

Present Situation

The most popular quality management strategy utilized globally is TQM. However, the Indian pharmaceutical sector does not employ it frequently. With nearly 20% of the world's total pharmaceutical product manufacturing, India is one of the biggest producers in the world. Because there are more small businesses in India than there are international corporations, TQM is only used there under limited circumstances. Furthermore, India has very few industries that are US-FDA or WHO-GMP approved. Due to a shortage of high-quality products, these small-scale firms prefer to export to underdeveloped nations like African nations. Poor quality is primarily caused by the ineffective deployment of quality management techniques like TQM. To improve quality, TQM should be strictly adhered to.

TQM: The principles and Methods

Definitions

TQM is an organization-wide initiative created to raise quality at every level. Customer-defined quality, or CDF, is what TQM is all about—meeting customer expectations for quality. To provide customers with high-quality goods and services, a business must work to create and maintain a culture of total quality management (TQM). TQM initiatives frequently rely heavily on the previously created quality control techniques. The following are various TQM definitions provided by international organizations:

According to British Standards Institution standard BS 7850- 1:1992, Total Quality Management (TQM) is a management concept and set of business practices that aims to utilize an organization's human and material resources in the most efficient strategy to meet the organization's goals.

According to International Organization for Standardization standard ISO 8402:1994, it is a management strategy for an organization that is quality-focused, built on the participation of all of its members, and aims for long-term success through customer satisfaction and benefits to all organization members and society.

This phrase was initially used to refer to a management strategy for quality improvement, according to The American Society for Quality. It's a management strategy for achieving long-term success through customer satisfaction, to put it simply. TQM is built on the idea that everyone in an organization should take part in enhancing its operations, goods, and culture.

Three further definitions of TQM are provided by the British Quality Association

1. The first focuses on intangible qualities and may be referred to as the "integrative management" concept, which aims to continuously improve the quality of goods and services by involving all levels and functions.
2. The second emphasis is on "hard" production/operation management, which leaves less room for employee discretion. A "collection of strategies and processes used to decrease or remove variation from a production/process or service delivery system in order to increase efficiency, reliability, and quality" might be used to describe it.

3. The third description combines hard and soft elements, and it has three characteristics: a fixation on quality, the necessity for a scientific approach, and the idea that all employees should be involved in this process.

Since those early days, TQM has changed significantly, and new innovations are always being introduced to the concept. Several definitions exist for TQM, including the following: "TQM is a management system and concept that aims towards ongoing organizational development in order to attain excellence and assure customer happiness and loyalty."

TQM is the ongoing process of identifying, minimizing, and ultimately eliminating manufacturing defects, optimizing the supply chain management process, enhancing the customer experience, and ensuring that staff are properly trained.

When it comes to organizational management, "TQM is a structured approach with a process focused on increasing the quality of an organization's outputs, including services and goods, by the ongoing improvement of its internal procedures."

The goal of TQM, an organizational management concept, is to constantly raise the caliber of processes and outputs.

The TQM strategy uses a combination of management and quality tools in an effort to both improve business and decrease loss brought on by faulty practices. It has been widely utilized in several industrial and service industries due to its high adaptability.

1. Focusing on the customer;
2. Analyzing processes;
3. Working in quality teams;
4. Systematically Analyzing Problems;
5. Implementing Planned Changes and Evaluating Results;
6. Using Data to Identify Problems and Solutions;
7. Implementing Changes

TQM emphasises continual improvement at all levels, from strategy to shop floor implementation. The main goal is to steer clear of errors and shield the goods from flaws. It aims to assure consistent quality by routinely improving staff, apparatus, workflow, and capabilities. The fundamental tenet of TQM is that errors frequently come from flawed systems and procedures rather than from people as a whole. It is possible to reduce such errors using three ways after determining their causes:

- Prevent mistakes from happening.
- Early identification to stop the error from causing damage farther along the supply chain where prevention is not possible.
- Immediate process correction if errors continue to occur.

Principals of TQM (Key elements)

To successfully apply TQM, an organization must concentrate on the following eight factors:

a) Ethics \s
b) Integrity \s
c) Trust \s
d) Training \s
e) Teamwork \s
f) Leadership \s
g) Recognition \s
h) Communication

Based on their functions, these eight elements are further divided into the following four groups:

Groups I and II are the "building bricks" and "binding mortar," respectively
Group III is the "communication" and "binding mortar," respectively
Group IV – Recognition, Roof

1. **Foundation**
   Building a culture of ethics, honesty, and trust is essential to fostering an inclusive workplace where everyone feels encouraged to participate. Ethics examines the good and bad in a situation from both an individual and an organizational perspective. Integrity is the frankness with which one sticks to the truth. The third component of the "basis," trust, which fosters a cooperative environment, develops when ethics are upheld with honesty.

2. **Constructing blocks**
   Employees must receive training in problem-solving and proper performance of their tasks. They must also receive social interaction training in order to improve teamwork inside the workplace. However, a team is only as good as its leader, who must provide motivating guidance and demonstrate a commitment to TQM on a regular basis.

3. **Binding Mortar**
   Communication, which refers to a shared interpretation of the message by the sender and recipient, is the thread that connects all of the TQM components. The effectiveness of TQM depends on open communication among employees as well as with vendors and consumers.

4. **Roof**
   The third component of TQM is acknowledging each individual's or team's contributions inside an organization. Employees who are recognized experience an increase in self-esteem and motivation, which in turn results in higher levels of production and quality.

Essentials for TQM implementation

1. Management's backing
2. Employee motivation and training
3. In-depth understanding of the causes and repercussions of the process

TQM: A comprehensive strategy

Research and development, production, and marketing are just a few of the different departments of the pharmaceutical industry that employ TQM to maintain quality. Figure 2 displays a number of TQM approach's features.

1. Research and development: TQM is extremely important for managing the quality of the research and development process. It involves the following:

a) GLP stands for "Good Laboratory Practices," as well. It entails stringent regulation of the use of animals in lab experiments. TQM in GLP includes

the following

- Creation of the study's protocol or master schedule sheet,
- Keeping a copy of the protocol in the lab where the study will be conducted,

Periodic inspection of the location where the study will be conducted; documentation and approval of any changes to the approved protocol of the study, along with a justification for the modification; and

- Documentation

Fig 2: Various TQM approach facets are shown

b). GCP stands for "Good Clinical Practices," as well. It entails stringent regulation of the use of humans in clinical trials. The GCP regulations are quite similar to the GLP requirements

The primary distinction is that in clinical trials, no subjects or people were involved before the investigation ever began. To ensure that individuals are aware they are participating in clinical studies, a fully completed, correctly filed informed consent form should be obtained from them along with their signature. Maintaining these documents is necessary. If patients withdraw from the study, the number of withdrawals and the reason for the withdrawal should be recorded.

Manufacturing: The process of making products, which includes the fabrication of dosage forms as well as the production of raw materials and API.

Post-marketing surveillance: This also covers quality management based on market research, or post-marketing surveillance. If any changes to the approved process are necessary, change control and associated documentation are involved.

Total quality management benefits

Total quality management is a term used to describe a coordinated organizational effort created to raise standards throughout the entire organization. A successful TQM programme has several advantages because it has also been characterized as the quest for excellence, fitness for use, value for money, customer happiness, etc. Financial advantages include the opportunity to charge higher pricing as opposed to competing ones, reduced costs, and larger returns on sales and investments. Hendricks and Singhai's ten-year analysis revealed a substantial correlation between TQM and financial performance. Other advantages include better access to international markets, increased customer retention rates, shorter development times for new inventions, and a reputation as a reliable company.

Because it takes a lot of time, effort, money, and patience to create a good programme, very few businesses employ TQM. However, implementing TQM can give businesses with the required resources a significant competitive advantage in their industry.

TQM in pharmaceuticals application

Total Quality Management is a technique that allows management and staff to participate in the process of production's ongoing improvement. It combines management and quality tools with the goal of boosting sales and decreasing losses brought on by wasteful behaviour.

An organization is seen by TQM as a collection of processes. It asserts that businesses should always endeavour to enhance these procedures by taking into account the skills and knowledge of their staff. Do the right thing, right the first time, every time is the straightforward TQM goal.

Total quality management

Total quality management (TQM), which is a genuine and significant attempt by an organization to modify its entire approach to business and make quality a guiding force in everything the organization does, has been dubbed as the

most widespread method of managing quality. The main components of TQM are covered in sections 3-5.

1. Strategic commitment: The foundation of TQM is the management's strategic commitment. Quality must first be understood as an objective goal that must be pursued, not only as an ideal, in the eyes of the company. Second, choosing to pursue quality comes with some significant costs, including the purchase of new buildings and equipment. Therefore, quality improvement will only be a term or gimmick without a commitment from senior management, with little to no actual change.
2. Employee participation: Another essential component of TQM is employee involvement. Almost all effective quality improvement initiatives entail holding the individual doing the job accountable for ensuring that it is done correctly. Employee involvement is, by definition, a key factor in raising quality.
3. Materials: Improving the caliber of the supplies used by organizations is another crucial component of TQM.
4. Technology: TQM programmes can potentially benefit from new technologies. Purchasing better equipment that can do tasks with greater accuracy and dependability frequently enhances quality.
5. Method: Better procedures can boost the calibre of goods and services. Methods are the operating systems that the company uses while undergoing the real change.

Process analysis, planning, and decision making management tools

For any process, activity, product, or service that is detailed, the environmental aspects and impact must be identified. The quality policy will need to be related to the objectives and targets. It is crucial to examine the organization's processes after developing the total quality management, vision, purpose, and value statements in order to offer the data required to create activity-specific policies, procedures, and work instructions for implementing TQM. Flowcharts, cause-and-effect diagrams, brainstorming, histograms, and other common decision-making tools, SWOT analysis, a Pareto diagram, and other tool**s** may be used in planning, evaluating, and ongoing improvement operations.

Cause-and-effect diagram

During a brainstorming session, different reasons for an effect are discovered. This results in the cause and effect diagram, also known as the CE diagram or Fish-Bone Diagram. For instance, the different factors that can influence any manufacturing process can be categorised into the so-called 4 M's, namely materials, men, machines, and methods. As a result, there can be significant variance in the quality of the finished product due to variations in the materials, machinery, staff, and procedures. Since these are the root causes of most manufacturing process problems, any TQM effort that employs this technique to examine them typically starts with them. Analysis of cost reduction is an example.

Brainstorming

There are numerous possible applications for this method in the ongoing improvement programme. Getting the proper group together and having them brainstorm can have incredibly great effects. Participants ought to be individuals who are impacted by the issue. "Quality circles" or "focus groups" are frequently used in high-quality programmes to provide ideas for new programme development and enhancement. These share a notion of brainstorming followed by data analysis. Brainstorming can be used to specific issues or be a regular element of daily tasks.

The FADE (Focus, Analyze, Develop, and Execute)

Approach, which was made popular by the total quality management (TQM) movement, is another method that can be used to expand on the concepts created during brainstorming. The participants concentrate on particular subjects, examine those subjects, create solutions, and put those solutions into action. The information created during brainstorming is organised and analysed during this procedure.

Pareto Diagram

Velfredo Pareto, an economist from Italy, found a rule in 1897 while researching the distribution of income. The guideline was later used by management gurus to apply to enterprises. Juran noted that a very small number of fault categories that result from a very small number of causes account for the majority of quality issues. Therefore, the quality issues are greatly reduced if these few crucial factors are investigated and controlled. According to organizational problem analysis, 20% of all causes account for 80% of all problems. Therefore, 80% of the issues can be resolved by resolving 20% of the causes. The "vital few" and "trivial many" principle or the 80/20 rule are other names for this theory. Experience has shown us that this is true in a number of areas of life.

The following is seen in the Pareto diagram

1. The percentage of defectives attributable to each source or cause
2. Identification of reasons that together account for a given percentage of defectives. Cumulative quantity or percentage of defectives.

Techniques for TQM

Various methods used by various industries in the TQM of the pharmaceutical industry include:

The Six Sigma Method

1. **DMAIC** is an acronym for a cycle of improvement that contains five phases. It is typically employed to enhance current company procedures. Figure 3 depicts the phases involved.
2. **DMADV:** It is employed in the development of new products or company procedures. It is an acronym for the development cycle, which consists of 5 Phases. Figure 4 depicts the various phases.

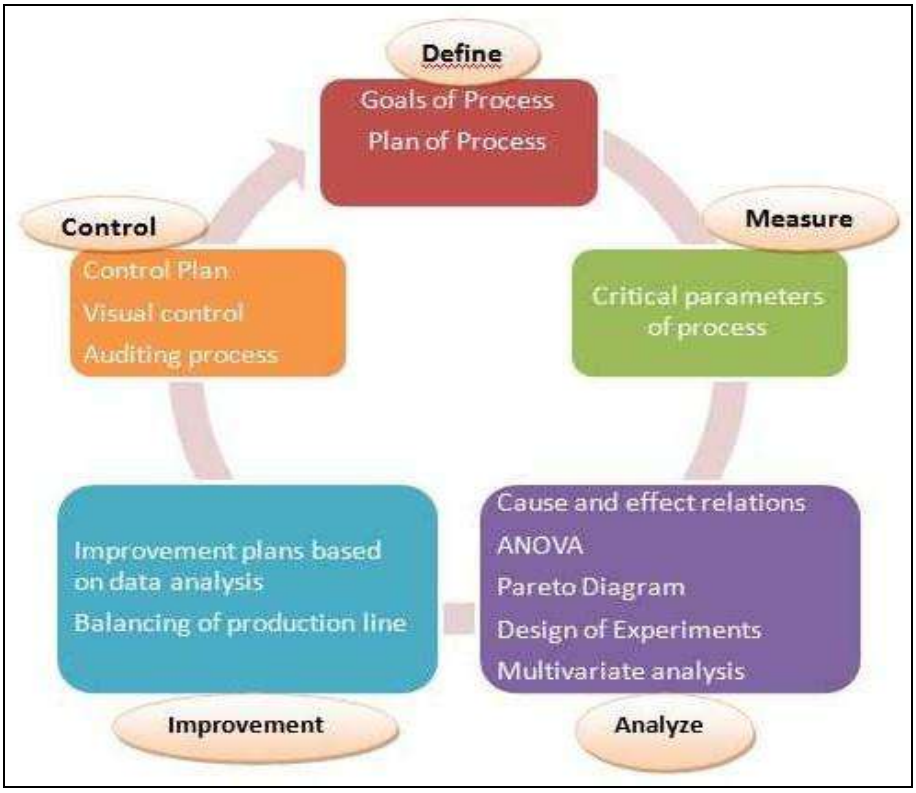


Fig 3: DMAIC

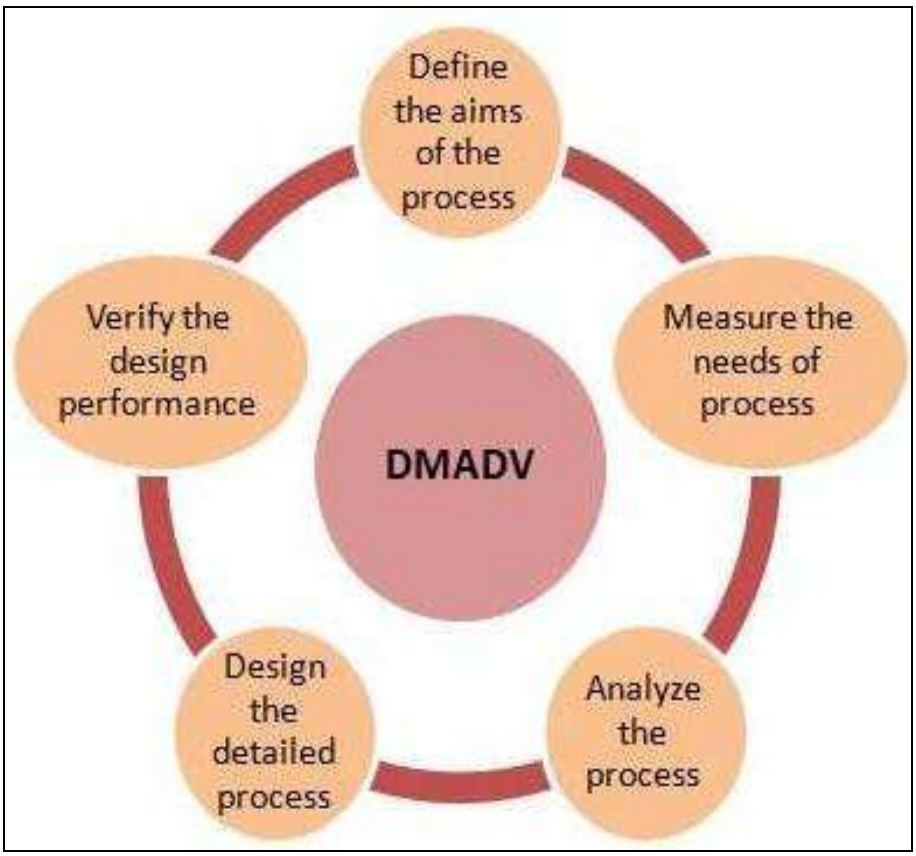


Fig 4: DMADV

Precision manufacturing

This phrase was originally used in 198817 by John Krafcik. Lean manufacturing primarily focuses on reducing three forms of waste, not many tools. Muda, Muri, and Mura are non-value-adding work, overburdening, and unevenness, respectively. 18

The fundamental goal of this strategy is to employ as little resources as possible that don't contribute to the final product's value, which in turn lowers costs and raises quality19. The term "lean" refers to a manufacturing process that minimizes waste output by putting the proper items in the proper locations to ensure a problem-free flow of

operations.

Quality risk management (QRM)

A system for assessing, controlling, communicating, and reviewing threats to the quality of pharmaceutical products is known as "quality risk management." Decisions can be made at any stage of the process. It is a frequently employed management strategy in the pharmaceutical industry that employs a systematic procedure for the discovery, analysis, and control of risk associated in any ongoing operation in the sector. Figure 5 depicts many components of quality risk management.

Risk identification is a crucial component of good risk management because it allows problems to be fixed before they become significant.

- Data analysis: This entails analyzing risk data and categorizing the risks according to their importance and impact.
- Planning: Making decisions on how to manage risks based on the analysis of risk data and planning for risk mitigation.
- Track: Keep tabs on the plans for risk reduction as well as the risk indicators.
- Control: To prevent deviation from these plans, strong control must be exercised over the risk mitigation strategy.
- Communication: It entails sharing comments on effective risk management strategies,
- their use in risk reduction and in identifying developing threats.

Quality by design (QBD)

Joseph M. Juran was the first to propose this idea. He claimed that planning may be used to build quality into a product. This method uses statistical analysis to optimize the constituent composition of a product. The US FDA has approved these statistical techniques for formulation optimization. Pharmaceutical Quality by Design (QbD) is described as "a systematic approach to development that begins with stated objectives and stresses product and process understanding and process control, based on strong science and quality risk management" in accordance with ICH Q8. A methodical, scientific, risk-based approach to pharmaceutical development known as pharmaceutical QbD starts with predefined ICH objectives. Design space is defined in Q8 based on the idea that quality must be incorporated into products from the outset.

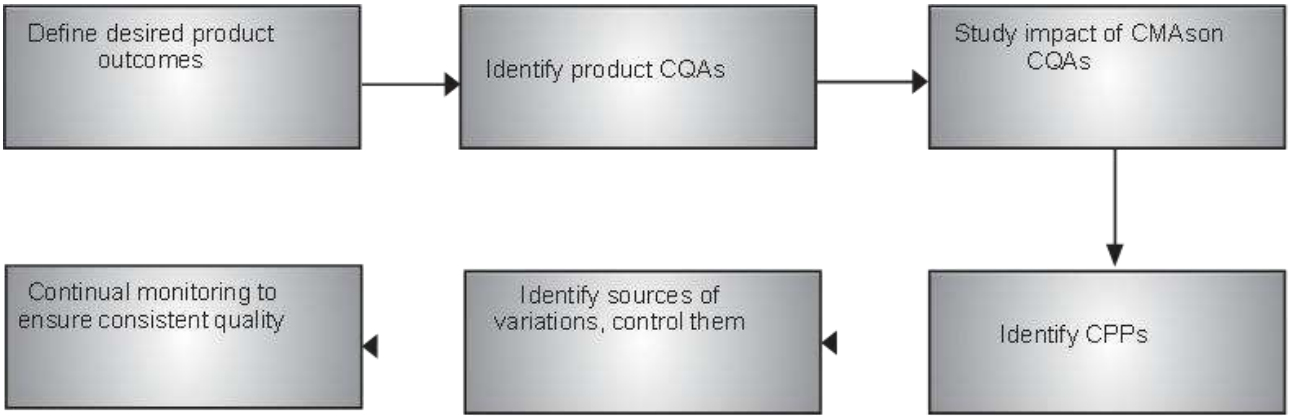
The QbD technique necessitates complete knowledge of the product and ongoing process, including important process parameters and quality features. It entails experiment design, which entails identifying crucial quality characteristics and process parameters. In a design space, it establishes the link between crucial quality traits and process factors. To consistently produce the product, a control strategy is developed. To obtain the desired quality, control over these characteristics is necessary.

Serie of ISO

The International Organization for Standardization created the ISO 9000 family of standards in 1987 to maintain an efficient system for quality assurance and quality management in manufacturing companies. The ISO 9000 standard is concerned with how an organization's quality management system is designed and implemented. This includes how the organization's business environment, changes to that environment, or risks associated with that environment, its varied needs, its unique objectives, the products it offers, the processes it uses, its size, and its organisational structure are all factors. This International Standard does not intend to suggest uniformity in the design of quality management systems or in the documentation.

Elements of QBD

1. The Quality Target Product Profile (QTPP), which identifies the CQAs of drug products.
2. Choosing critical material attributes for product design (CMAs).
3. Defining critical process parameters and designing processes (CPPs). This includes integrating CMAs, CPPs, and CQAs.
4. The development of specifications for active pharmaceutical ingredients (APIs), excipients, and the finished drug product as well as controls at each stage of the manufacturing process constitute the controls strategy.
5. Process flexibility and ongoing development.



1. The Quality Target Product Profile (QTPP)

The QTPP is a list of the quality criteria that a pharma product must meet in order to be of the intended quality. On this foundation, product design will start.

1. The intended use of the product, its route of administration, desired dosage form, and drug delivery method are all factors to be taken into account while designing the QTPP.
2. The dose's strength.
3. The chosen container-closure system.
4. The therapeutic component's release and variables that would affect pharmacokinetic characteristics (such the drug's dissolution) in the suggested dosage form.

5. The final product must meet quality standards for stability, purity, sterility, drug release, etc.

2. Choosing critical material attributes for product design (CMAs)

The CQAs of the drug product can be determined after the QTPP is complete. CQAs are characteristics of the final product—physical, chemical, biological, or microbiological—that must fall within a specific range, limit, or distribution to guarantee that the intended level of product quality is reached.

The identity of the medication, assay results, content uniformity, drug release profile, degradation products, microbiological levels, moisture content, and physical characteristics including size, colour, shape, and friability are a few examples of quality aspects of drug products. Some of them might not be essential qualities. The severity of the harm that may result from a product deviating from that attribute's permitted range determines whether or not that attribute is critical.

3. Defining critical process parameters and designing processes (CPPs). This includes integrating CMAs, CPPs, and CQAs

Clinical research can attest to the fact that a well-designed product satisfies patient needs. Stability studies can attest to the performance of such a product over the course of its shelf life. Therefore, product design must be focused on creating a sturdy product that provides the target QTPP for the duration of the product's shelf life.

The following topics need to be thoroughly studied for excellent product design:

- The drug's physical, chemical, and biological properties, such as its solubility, melting point, pKa, oxidative stability, partition coefficient, bioavailability, membrane permeability, and particle size.
- The excipients' grade, type, and information on their inherent variability (common excipients such as binders, diluents, disintegrants, glidants, coloring agents, sweeteners, suspending agents, film coatings, preservatives, flavors etc.).

• Excipient interactions discovered by testing for drug-excipient compatibility.

• The critical material attributes (CMAs) of the medicine and the excipients to guarantee the creation of a stable formulation.

CMA vs CQA

CMA: Physical, chemical, biological or microbiological characteristic of raw material
that must lie within appropriate limits or range to ensure desired quality.

CQA: Physical, chemical, biological or microbiological characteristic of drug product intermediates or finished drug products that must lie within appropriate limits or range to ensure desired quality.

Process Design

To produce a drug product, a manufacturing process is made up of a number of unit operations that are carried out in a specific order. Any activity that causes a substance to change physically or chemically is referred to as a unit operation. Unit activities used in the production of tablets include milling, mixing, granulating, drying, compressing tablets, and coating.

To produce the required product, processes must be designed so that each unit activity is carried out as expected. For this, it's crucial to

a) pinpoint the key reasons of variations.
b) Control these variations while the process is ongoing.
c) Accurately and dependably predict the product's quality attributes.

Any parameter whose variability could negatively affect a CQA is a critical process parameter and is referred to as such (CPP). Prior to monitoring and regulation, all CPPs for a particular process must be recognized in order to ensure the production of products of the desired quality.

To determine whether a process can withstand variation in the input materials and processing parameters and still produce a result of an acceptable quality, process robustness studies must be carried out. These investigations will help to find CPPs that affect the caliber of medicines.

Table 1: Evaluation of CMAs, CPPs and CQAs for unit operation of tablet compression

CMAs	CPPs	CQAs
Particle size distribution	Type of press Design of hopper, vibration, height Feed mechanism 0-force feed/gravity feed, rotational direction Tool design – metal quality, score configuration Maximum punch load Pressing speed Compression force (pre, main) Penetration depth of punch Dwell time Ejection force	Appearance of tablet
Proportion of oversize/fines		Tablet weight and uniformity
Shape of granules		Hardness
Cohesive properties		Friability
Hardness		Content uniformity
Density values – bulk/tapped/true		Thickness Tablet density/porosity
Electrostatic properties		Defects
Brittleness		Disintegration time
Moisture content		Moisture content
Polymorphism		Dissolution profile

1. List all process parameters that may impact the process performance
2. Using scientific knowledge and risk assessment, identify the parameters that are potentially high risk
3. Establish ranges for these high-risk potential parameters
4. Design and carry out experiments to test these parameters
5. Obtain experimental data and analyze it using first principle models to confirm how critical the process parameter is. Connect CPPs and CMAs to CQAs wherever possible
6. Develop a control mechanism by defining acceptable ranges for critical parameters and non-critical parameters.

How to understand processes?

Control Plan

A control strategy must be established using the information gathered during developmental investigations. It is typical to have controls at the following three levels:

Level 1: Real-time monitoring of CQAs of the output materials is carried out using automated engineering controls. The system is intended to track the characteristics of the input material and automatically alter the process settings to ensure that CQAs consistently meet the predefined standards of approval. Systems using Process Analytical Technology (PAT) are an illustration of this kind of control.

Level 2: At this level, the focus is on comprehending the product and the procedure in order to develop it with control over the pharmaceutical process. This is QbD, which permits the control of variables and so ensures the quality of the drug product.

Level 3: This method, which is used in traditional pharmaceutical manufacturing, depends on thorough testing of the final product. The possibility of product issues is high since the sources of variability have not been identified and because CMAs and CPPs have not been studied in relation to the quality of drug products.

In practical settings, it is preferable to combine level 1 and level 2 control tactics to create a hybrid strategy that includes.

1. Controlling input material qualities based on research into their effects on product quality and process ability.
2. Setting up product requirements.
3. Having the most significant unit operations that affect product quality under control.
4. Rather of depending just on end-product testing, test while in-process, in real-time.
5. Implementing a monitoring programme to confirm that the procedure and output are under control.

Process capacity and on-going development:

When compared to the predetermined acceptance criteria, a stable, controlled process's amount of inherent variability is measured as process capacity. The QbD programme must lead to the detection and reduction of differences that have an impact on the product's quality, whether they are short-term or long-term.

Methods of continuous improvement must be used to eliminate these sources of variability. This encompasses a variety of actions in various stages, including:

1. Outlining the issue and establishing precise objectives
2. Assessing crucial process variables and gathering information
3. Using data analysis to identify cause-and-effect connections
4. Use data analysis findings to improve the procedure.
5. Run pilot operations to test the capabilities of the optimised process
6. Keep track of procedures to ensure that they remain under statistical control.

Tools of QBD

Utilizing specific tools is necessary for Quality by Design.

Prior knowledge, risk assessment, mechanistic models, experiment design, data analysis, and process analytical technologies are a few of these.

1. Prior Information

According to ICH rules, prior knowledge includes information, knowledge, or skills that have been picked up via prior experience with processes identical to those in question and published data. The tool can be used from the start of the development process and updated on a regular basis utilising the data produced by the process. In regard to QTPP and CQAs, prior information may be utilised as part of control strategies. However, it's crucial to avoid placing an excessive amount of dependence on existing information because doing so could give up control over the production process.

2. Risk Evaluation

Prior to development studies, quality risk management must be carried out in accordance with ICH Q9 in order to identify high-risk factors that affect the quality of drug products. Critical variables are frequently chosen through risk appraisal, which must be carried out in accordance with scientific understanding. To build a control plan, these factors must then be further examined through

experimentation.
Flowcharts, fault tree analysis, failure mode impacts analysis, hazard analysis and important control points, risk ranking and filtering, etc. are some of the frequently used risk assessment tools.

Failure Mode Effect Analysis (FMEA)
Failure mode refers to the defects or errors in a material, equipment, design or process. After establishing these failure modes, the tool evaluates their effects, and ranks them in order of priority. This method may also include a study of how critical the consequences of the failures are. Sometimes, Ishikawa diagrams (fishbone/cause-and-effect) are also used.

Hazard Analysis and Critical Control Points (HACCP)
Hazards that can cause safety and quality issues are identified (for example, hygiene of personnel, material flow, environmental aspects, process design, manufacturing steps). Preventive measures for each of these are established. Next, critical control points are determined for these hazards, and limits are established. A system is set up to monitor these critical control points, and corrective actions to be taken when these are not in a state of control, are determined. Finally, record-keeping systems are set up to monitor and confirm that the HACCP system itself is working as expected.

FMEA and HACCP
Experiment design
With this tool, a process's variables are changed in a deliberate manner through the setup of a number of structured tests. The effect of these adjustments on a selected output is then evaluated. This tool is quite good at figuring out all the variables that together affect the output replies. It is also possible to quantify how the variable factors interact. Analytical

3. Process Analytical Technology (PAT)
PAT is described by the US Food and Drug Administration as "A system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."
PAT makes it possible to monitor CMAs, CPPs, or CQAs in real-time to show that the process is under control. Online measurements made possible by it are particularly helpful for identifying failures, It permits changing the operational settings when variations that have a detrimental influence on the quality of the produced are discovered.
A wide range of tools are included in PAT to collect physical, chemical, microbiological, analytical, and mathematical data and conduct risk assessments. PAT aids in the control of process parameters as well as product quality by establishing an interface between the process and the instrument as well as a feedback loop that can alter processing conditions.

QBD Advantages
1. Better product quality assurance as a result of enhanced process design and better quality risk management during the production process.
2. Cost reductions are a result of innovation, better efficiency, and decreased error potential.
3. Enhances compliance with regulations and streamlines change management.
4. As opposed to the customary end-testing of completed products, real time testing during the process promotes speedier releases.

Issues with QBD
1. Requires a change in the organisational approach to quality's cultural foundation.
2. Expensive; managerial support is needed.
3. Requires departmental cooperation, yet there can be resource or workload constraints.

In conclusion, QbD may be viewed as a quality system that supports the management of a product's life cycle. It promises to lower the risk of patients taking drug goods by focusing on building a competent process through improved product and process understanding. In order to produce high-quality drug products that consistently fulfil their quality criteria, the focus of QbD is on continuous improvement, drawing on prior experience, employing risk management strategies, and recording knowledge.

Current Good Manufacturing Process (CGMP)
This is another method for managing the quality of medications. Several organisations, including the US FDA, WHO, and the European Medicines Agency schedule M in India, have provided guidelines for acceptable manufacturing methods. These include recommendations for selecting a location, amenities, accommodations, attire, a disposal system, sanitation, testing, recording analysis, documenting any reprocessing or recall, and filing change controls if a process change occurs. Therefore, in order to ensure that the product is of high quality, it is essential to have a complete understanding of the good manufacturing practises used in the process.
The International Conference on Harmonization (ICH) has developed Q9 recommendations for pharmaceutical product development and Q8 guidelines for quality risk management of pharmaceutical goods (R2). Risk assessment, risk management, and various techniques for quality risk management, including failure mode and effect analysis (FMEA), failure mode, effects, and criticality analysis (FMECA), hazard analysis and critical control points (HACCP), preliminary hazard analysis (PHA), risk ranking, and filtering, are covered in Q9 guidelines.
Therefore, TQM of the process is achieved through a variety of methodologies, including six sigma, lean manufacturing, quality risk management, quality by design, ISO, cGMP, ICH, etc. Strong and appropriate documentation systems are the fundamental TQM tool since every quality management system is inadequate without adequate or thorough documentation. Because it is a well-known adage that "anything not written or documented means not done". Consequently, for full TQM implementation, Everything must be adequately documented and presented in a way that is both readable and understandable. A good change control or deviation control should be filed and approved for every modification or deviation from the validated procedure, specifically if there is any process change or deviation.
Modern technological developments that support TQM
Real-time quality management of pharmaceuticals using automated methods
Many industries employ a variety of automated methods to

ensure quality at various stages of a process. These are components of the TQM approach because they eliminate the need for testing and sampling at various stages. Instead, analyzers and probes provide automatic readings at each operation and inform computers whether the process is ongoing or not, which increases productivity by reducing testing and sampling requirements.
Following are a few examples of such automated methods for real-time quality management:

AOTF Multiplexed Analyzer by Brimrose
For a variety of process applications in the pharmaceutical, food & dairy, chemical, polymer, petrochemicals, agricultural, pulp & paper, wine industries, and military, Brimrose's tough and high performance on-line AOTF NIR process spectrometers provide quick responses and multi-component analysis. Acoustic diffraction of light in an isotropic medium is the foundation of the optical device known as an AOTF. Currently employed as a quantitative method, near-infrared spectroscopy (NIR) relies on chemometrics to provide calibrations. These spectrometers can scan extremely quickly and without the use of moving parts thanks to AOTF technology. Because of this, it is the perfect instrument for on-line, real-time industrial process control. These analyzers are designed to function dependably even in tough production conditions over an extended period of time and meet all specifications and regulations for online applications. The following benefits of this technology over traditional approaches:
• Rugged, little gadget • Lacks moving parts, vibration-resistant
High signal-to-noise ratio; ability to function in adverse conditions measuring diffuse reflectance
For crystalline or powdered materials, it is a superior sampling technique in the mid-IR and NIR (near-infrared) spectral regions. They can be used to keep tabs on a continuous action or reaction.

Probes for CIP and WIP
Clean in place is another name for CIP. Equipment needs to be cleaned with the operator's involvement being minimal. Wash in place is another name for WIP. The probes that keep track of this cleaning in place and washing in place procedure are called CIP and WIP probes.
The following are some advantages of CIP and WIP probes:

- Results are reproducible, repeatable, and controllable; • Procedures are verifiable;
  Reduced cleaning time, automatic cycles that guarantee each item is cleaned thoroughly each time,
- Lessening the handling of chemicals;
- Saving money on chemicals, water, and effluent, as well as labour costs,

Better health and safety, batch traceability and record keeping, and the capacity to utilise more potent chemicals and greater temperatures, among other things.

Sensors - Based packaging Technologies
Pharmaceutical packaging using sensors-based technology has created new opportunities for online and in-process packaging process monitoring. The following list of recently used sensors includes some of them:

Ultrasonic fill level measuring sensor
These sensors are used to gauge the process's fill level. These are the sensors that can withstand high pressure and high temperatures. However, these sensors' sensitivity varies with temperature since temperature changes also affect how quickly ultrasonic waves travel. Therefore, while designing a system to alter the speed of ultrasonic waves, temperature monitoring systems should be considered.

Product presence detection using fibre optic sensors in packaging
It is made up of a fibre optic wire and an amplifier. These sensors detect the presence of product in the packaging. For example, in tablet packaging, if any cavity is empty, a signal that there is no product in the cavity will be sent. In automated processes, if this issue persists frequently, the procedure is stopped. It has a very high switching frequency and is simple to use. tiny background-suppression sensor for content surveillance
These photoelectric sensors are utilised for a variety of cutting-edge tasks, including background occlusion, transparent object identification, contrast sensors for colour marking, etc. In this, product detection is colour-independent. Sharp background suppression is produced, allowing for extremely accurate product detection. These sensors are also employed in web edge monitoring, which keeps an eye on the packing material's edge while it is being packaged.

Ultrasonic sensor for detecting sticky strips
These are ultrasonic sensors, which utilise ultrasonic waves to identify adhesive strips on product packaging. It determines whether or not the sticky strip is still intact.
methods to prevent counterfeiting
The following are some of the several methods employed by the pharmaceutical industry to identify phoney medications and counterfeit drugs:

Holographic method
It is a method that offers consumers a straightforward way to evaluate the legitimacy of a medicine. The interference patterns produced by the interplay of laser beams are what create holograms. Security holograms that are now accessible create 2D and 3D graphics. Holograms are now frequently used to identify the "correct product" and come in a variety of formats, including holographic shrink sleeves, holographic induction cap seals, and holographic hot stamping foil.

Identification using radio waves (RFID)
It is based on an electronic chip that produces radio frequency waves encoded with a particular ID or code47, making it one of the most promising authentication technologies. Through card readers48, these specialised chip readers are utilised to capture the code as the products move through the supply chain. The main benefit is that line of sight is not necessary. But this technology's biggest flaws are its expensive price, readability, and lack of item-level security.

The use of widespread encryption (Mass encryption technology)
It is a method for giving each product produced by a computer-based encryption engine a distinct digital identity.

Because each piece of digital encryption can be given a different unique code, it is significantly more secure. The 16-digit alphanumeric number used to represent the encrypted code is printed on the packaging during manufacturing, giving each drug a distinct identification. An important benefit of this technology is that customers may easily confirm the legitimacy of the drug by using the codes printed on blister packs, entering the codes online, or sending SMS messages with the codes.

Conclusion

The best instrument for pharmaceutical quality control is TQM. Although it is strongly advised by many regulatory authorities, it is not yet fully adopted in many businesses, particularly in India. Since India is one of the world's top exporters of pharmaceutical items, proper TQM adoption is essential in the Indian setting. Despite significant progress being made in product development for real-time online production and packaging monitoring, the bulk of sectors still only use them sparingly, which is a major cause for concern. This essay is an appeal to the pharmaceutical industry and international regulatory bodies for stronger enforcement and serious adoption of TQM principles in industries with a view to providing high quality medications.

The primary accountability for the calibre of his products rests with the pharmaceutical maker. Pharmaceutical makers are under enormous professional, societal, and legal obligations to guarantee the quality of their products. It should be understood that without systematic implementation of good manufacturing practises (GMP) and strict process control, no amount of dosage form testing and control can maintain and secure product quality. The only way to ensure the quality of the final product is through well planned, well-executed process and dosage form control before, during, and after production. Product quality must be ingrained rather than only tested in the finished item.

The producer ought to be in a position,

a) To manage the factors materials, equipment, processes, and people—that cause variation in product quality.
b) To guarantee the most suitable and accurate manufacturing and packaging procedures.
c) To ensure that the testing outcomes adhere to the standards or requirements.
d) Using a comprehensive complete quality assurance system to ensure product stability and carry out other tasks connected to product quality.

Certain fundamental operating principles should be created and should always be followed for the overall quality management system to operate properly. First, all decisions regarding control must be made purely on the basis of the product's quality. The operation must also strictly comply to the established standards or specifications as decided through systemic inspection, sampling, and testing, and it must constantly work to raise the bar for the current standards or specifications. Third, it is important to fully supply the resources, environments, and facilities needed for staff to carry out their duties. Last but not least, control decisions should be made independently administratively and under no circumstances should they submit to or be overridden by production or marketing. The environment required for wise decision-making is crucial because the control decision may affect both the consumer's health and the manufacturer's reputation. Only the highest level of management should examine the control decision during times of significant disagreement.

References

1. Enders JE. Quality assurance and control, In: Gennaro A. R. (Eds), Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, New York. 2000;1:980-985.
2. http://www.5squalityposters.com/blog/?p=15 accessed on 8/4/2014.
3. Lachman L, Hanna SA, Lin K. Quality control and assurance, In: Lachman L, Lieberman H. A, Kanig J. L. (Eds.), The theory and practice of industrial pharmacy, Verghese Publishing House, Bombay, 1976, 804-855.
4. Wikipedia the encyclopedia, http://en.wikipedia.org/wiki/Quality (business) accessed on 2/2/2014.
5. Rose. Kenneth H. Project Quality Management: Why, What and How J. Ross Publishing, Fort Lauderdale, Florida, 2005, 41.
6. http://www.academy-for-leaders.com/blog/post/61 accessed on 8/4/2014.
7. Mandal SK. Introduction to TQM: In TQM, Principles and practice, Vikas publishing house, New Delhi, Second reprint, pp. 1-18.
8. Lakshmana Rao, Bharani M, Madhu Y, Sankar GG. TQM: The Need of New Era, Indian J Pharm. Educ. Res. 2005;39(4):203-206.
9. Wikipedia the encyclopedia, http://en.wikipedia.org/wiki/Total_quality_manage ment accessed on 3/2/2014.
10. Choda SR. ISO: 9000 Quality management systems in pharmaceutical sector. Pharma Times. 2003;35(1):7-11.
11. Hoyle and David. Quality Management Essentials, Oxford, United Kingdom: Butterworth- Heinemann, 2007, 200.
12. Pfeifer and Tilo. Quality Management: Strategies, Methods, Techniques, Munich, Germany: Carl Hanser Verlag, 2002, 5.
13. Rao AL. TQM: The need of new era, Indian Journal of Pharmaceutical Education. 2005;39(4):203.
14. Bhaskar M, Sanjib B, Abhishek Y. TQM in pharmaceuticals: A review, Int. J Pharm Tech Res. 2011;3(1):365-375.
15. Kanji GK. Total Quality Management Proceedings of The First World Congress. Chapman & Hall, London; c1995.
16. Sharma RS, Gupta SK. Business Organisation and Management, 2nd Ed., Kalyani Publishers, New Delhi. Moy, A. 2009. EMEA and FDA approaches on the ICH Q10 on pharmaceutical quality system. Pharma Times. 2009;41(8):15-18.
17. Subrahmanyam CVS. Pharmaceutical Production and Management. 1st Ed., Vallabh Prakashan, New Delhi; c2009.
18. Case N. Six Sigma Black Belts stamp out tough quality problems, Quality on line, 1999, available at http://qualitymag.com/articles/1999/aug99/0899 f3.html accessed on 25/2/2014.
19. http://www.isixsigma.com/new-to-six- sigma/design-for-six-sigma-dfss/dmaic-versus- dmadv/ accessed on 8/2/2014.

20. De Feo, Joseph A, Barnard W. Juran institute's six sigma breakthrough and beyond - quality performance breakthrough methods, Tata McGraw- Hill Publishing Company Limited; c2005.
21. Krafcik JF. Triumph of the lean production system, Sloan Management Review. 1988;30(1):41-52.
22. Ohno T. Toyota Production System, Productivity Press, 1988, 8.
23. Womack J, Jones DT, Roos D. The machine that changed the world: the story of lean production, HarperCollins Publisher; c1990.
24. Nave D. How to Compare Six Sigma, Lean and the Theory of Constraints, A framework for choosing what's best for your organization, Quality Progress-March, American society for quality; c2002.
25. Griffith E. Risk management programs for the pharmaceutical industry, Fujitsu Consulting, white paper, Pharmaceutical industry; d2004.
26. ICH Q9. Quality risk management; c2005.
27. Wikipedia the encyclopedia, http://en.wikipedia.org/wiki/Quality_by_Design accessed on 6/4/2014.
28. "ICH Q8 (R2)," Pharmaceutical development; c2009.
29. Kumar S, Baldi A. Design of experiment based statistical optimization in life science research: An overview, Pharm Aspire. 2013;4:35-43.
30. Kumar S, Thakur S, Tanwar D, Baldi A. A quantitative approach for pharmaceutical quality by design patterns, Inventi Rapid: Pharm Analysis & Quality Assurance. 2012;4:1-8.
31. Wikipedia the encyclopedia, http://en.wikipedia.org/wiki/ISO_9000 accessed on 6/4/2014.
32. http://www.econ.canterbury.ac.nz/downloads/busgwp.pdf accessed on 6/4/2014.
33. ISO 9000. Introduction and Support Package: Guidance on the concept and use of the process approach for management systems, http://www.iso.org/iso/04_concept_and_use_of_the process_approach_for_management_systems.pdf accessed on 6/4/2014.
34. Quality management system for active pharmaceutical ingredients manufacturers http://apic.cefic.org/pub/2QualityMgtSystGMP9712.pdf accessed on 6/4/2014.
35. "WHO," guidelines on good manufacturing practices for herbal medicines, 2007, available at http://apps.who.int/medicinedocs/documents/s14215e/s14215e.pdf accessed on 16/4/2014.
36. http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm090016.html accessed on 16/4/2014.
37. "Schedule M," Good manufacturing practices and requirements of premises, Plant and equipment for pharmaceutical products, Gazette of india, Extraordinary, part ii-section 3, sub-section (i), Ministry of health and family welfare (department of health) New delhi, 2001, available at http://www.rajswasthya.nic.in/Drug%20Website%2021.01.11/Revised%20Schedule%20%20M%204. pdf accessed on 16/4/2014.
38. Karmacharya JB. Good Manufacturing Practices (GMP) for Medicinal Products, available at http://cdn.intechopen.com/pdfs-wm/37170.pdf accessed on 16/4/2014.
39. De Marinis MG, Piredda M, Pascarella MC, Vincenzi B, Spiga F, Tartaglini D, *et al*. 'If it is not recorded, it has not been done!'? consistency between nursing records and observed nursing care in an Italian hospital, J Clin Nurs. 2010;19(11-12):1544-52.
40. https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&ved=0CD8QFjAA&url=http%3A%2F%2Fwww.fda.gov%2Fohrms%2Fdockets%2Fac%2F02%2Fbriefing%2F3841b1_06_astrazeneca.ppt&ei=i0rvUoHPEo6MrgftuIGoCA&usg=AFQjCNGeecaVZk58yE2nMfWGcPpYXj5OrA&sig2=j1d0QkUXBhDyXyA6QN7Ww&bvm=bv.60444564,d.bmk accessed on 3/2/2014.
41. http://www.brimrose.com/products/nir_mir_spectrometers.html accessed on 6/3/2014.
42. http://www.piketech.com/files/pdfs/DiffuseAN61 1.pdf accessed on 6/3/2014.
43. http://people.bath.ac.uk/gp304/uv/44-74668PRD_DiffuseReflectanceTransmittance.pdf accessed on 6/3/2014.
44. http://www.ciprocess.co.uk/pdfs/CIP%20Introduction.pdf accessed on 6/4/2014.
45. https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=15&cad=rja&uact=8&ved=0CKkBEBYwDg&url=http%3A%2F%2Fwww.springer.com%2Fcda%2Fcontent%2Fdocument%2Fcda_downloaddocument%2F9783319006321-c2.pdf%3FSGWID%3D0-0-45-1404760-p175159475&ei=DMMuU8T4E8qZiAeqkoB4&usg=AFQjCNEqZ78wp65ukXw-_EPunAThyN-KRQ&sig2=kSr7j19YqBF9vIO_aTKEg&bvm=bv.62922401,d.aGc accessed on 23/03/2014.
46. http://www.aelectric.com/pdfs/takex/Sample_applications.pdf accessed on 23/3/2014.
47. http://www.directindustry.com/prod/datalogic-automation/miniature-diffuse-reflection- photoelectric-sensors-background-suppression- 40572-419014.html accessed on 23/3/2014.
48. http://files.pepperlfuchs.com/selector_files/navi/productInfo/doct/tdoct0799c_eng.pdf accessed on 12/3/2014.
49. Bera A, Mukherjee A. The importance of generic drugs in India, IJPCBS. 2012;2(4):575-587.
50. Ruchir Y, Prajesh N. Anticounterfeit packaging technologies, J Adv Pharm Tech Res. 2010;1(4):368-373.
51. Magnar DY, Chaudhuri A. Counterfeit drugs problems and solutions for the Indian pharmaceutical industry. 2009;5:1-6.
52. Mackey TK, Liang BA. The global counterfeit drug trade: Patient safety and public health risks, J Pharm Sci. 2011;100:4571-4579.