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### TOTAL QUALITY MANAGEMENT OF PHARMACEUTICALS: RECENT APPROACHES AND ADVANCEMENTS

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#### **ABSTRACT:**

Quality of pharmaceuticals has always been a prime area of concern for regulatory agencies across the globe in order to facilitate production of medicines without batch to batch variations and hence maintaining the same therapeutic effectiveness with the advent of total quality management a new vista has opened for assured quality of pharmaceuticals. Total quality management being a multidimensional approach essentially requires adherence to quality practices in all areas of pharmaceutical production. Application of various approaches and practices *viz.* quality by design, quality risk management, six sigma approach along with following regulatory guidelines in all facets may lead to practical realization of this concept. This article presents a brief review of existing industrial practices of total quality management with special emphasis on recent advancements in online production monitoring, sophisticated analytical tools and anti-counterfeiting technologies.

**Keywords:** Counterfeit drugs, Good manufacturing practices, Lean manufacturing, Quality, Quality by design, Quality risk management.

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#### **INTRODUCTION**

Pharmaceutical industry is a very vital segment of the our health care system, which deals with manufacturing and marketing of pharmaceuticals and biological products and medicinal devices, used for the diagnosis and treatment of diseases as well as conducts research for development of new products for human welfare. So maintenance of quality is very necessary to prevent health hazard as many pharmaceutical products are life saving products, so if products are not of appropriate quality then they may result in severe adverse effects or even death of the consumer or patient. Regulatory agencies of various countries noted that there are deficiencies in conventional quality management systems, so they start adopting this approach called Total Quality Management (TQM). This concept of TQM is very important for maintenance and improvement of quality and for prevention of defects<sup>1</sup>. Initially concept of total quality control was used that quality was

assured just on basis of quality control parameters quality was assured. But this concept of TQM involves building quality in a pharmaceutical product as it involve complete records such as standard operating procedures for every step, validation records, master formula records and batch production records etc. This review includes information about quality, quality management, current status and need of TQM. This article describes TQM as multifaceted approach for quality management of pharmaceuticals by utilizing various quality management approaches such as quality by design, good manufacturing practices, quality risk management etc. leading to high quality products.

#### **Quality**

The term quality is used very commonly, this term looks to be very easy but it is difficult to define quality precisely.

- As per ISO, it is defined as “Degree to which a set of inherent characteristics fulfills requirements”. Degree refers to a level to which a product or service satisfies. So, depending upon the level of satisfaction, a product may be termed as excellent, good or poor quality product. Inherent characteristic are those features that are a part of the product and are responsible to achieve satisfaction. Requirements refer to the needs of customer, needs of organization & those of other interested parties<sup>2</sup>.
- Quality has been defined in different ways by the quality gurus as conformance to standards or specifications; fitness for use; meeting customer’s requirements or expectations etc<sup>3</sup>.
- Quality may also be defined as non-inferiority or superiority of a product.
- Quality is a perception which may be understood differently by different people.

The quality can be of two types

**Specification quality**

This is quality from consumer point of view that how consumer compares it with other products in the market.

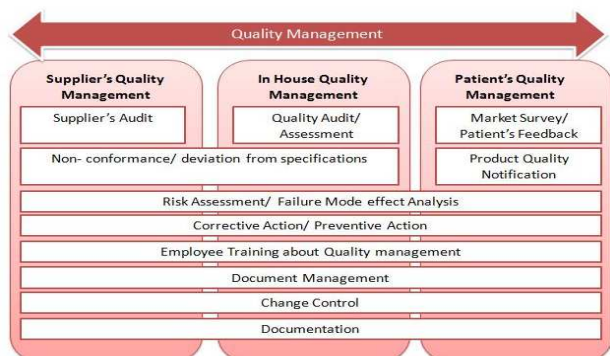
**Conformance quality**

It is the measure of degree to which product or service was produced correctly.<sup>4</sup>

As per pharmaceutical industry, quality is defined as conformance to specifications of the product. The specifications are different for different products depending upon its therapeutic effect, potency etc.

**Quality Management**

Quality management is management of various sectors to ensure good quality of the product. Quality management consist of four main components i.e. Quality planning, Quality control, Quality assurance, Quality improvement<sup>5</sup>. The outline of quality management system is given in Figure 1.



**Fig. 1** Outline of Quality management system

**Practices before TQM**

Before existence of TQM, traditional quality management tools, only included final product quality

control (FPQC) and on basis of these quality control tests, it was concluded that whether product obtained is of desired quality or not. If all parameters of final product were found to be within limit, then it was considered as quality product but if results were found to be out of specifications then product was said to be of poor quality and rejected. Main drawbacks of traditional methods were that they do not include any process or steps for quality management of product during the process. Only quality control department was responsible for quality of the product, other departments were having no concern with the quality, which usually result in batch-to-batch variability<sup>6,7</sup>.

**Evolution of TQM**

As in conventional systems, quality only depends upon final product quality control testing. They resulted in increase in cost and time consumption as detection of the problem is only possible at the end of the process. Scenario changed with change in evolution and application of TQM, i.e. every department is concerned with quality management of product. Quality is checked at every step in the process and if any problem arrives it is tried to be solved at that moment only. Quality does not depend only on final product quality control testing it is monitored in every step. So it also resulted in increase in quality of the product and also saves cost and time involved due to batch failure or due to solving a problem involved in the process. So TQM should be implemented by pharmaceutical industries as it result in increase in quality of the product, which is very necessary as pharmaceutical industry is most vital part of healthcare system and also decrease time involved in production, which ultimately result in decreasing cost of product.

**Current Status**

TQM is most widely used quality management approach worldwide. But it is not used widely in Indian pharmaceutical industry. India is one of the largest producers of pharmaceuticals in the world with about 20% of total production of pharmaceuticals product in the world. The main reason for restricted application of TQM in India is that, number of small scale companies is more than the number of multinational companies. Furthermore the number of WHO-GMP or US-FDA certified industries is very less in India. These small scale industries prefer to export to poor countries such as African countries because of lack of quality products. The main reason for poor quality is incomplete application of quality management approaches such as TQM. So TQM should be followed strictly to increase quality.

**TQM: The Concept and Approaches**

**Definitions**

TQM is a combined effort designed by organization to improve quality at every level. TQM is about meeting quality expectations as defined by the customer; this is called customer-defined quality<sup>8</sup>. TQM consists of efforts of organization to install and make a climate in which an organization continuously improves its ability to deliver high-quality products and services to consumers. TQM efforts typically depend mainly on the previously developed techniques of quality control<sup>9</sup>.

Various definitions of TQM given by global organizations are as follows:

As per British Standards Institution standard BS 7850-1:1992, TQM is a management philosophy and company practices that aim to harness the human and material resources of an organization in the most effective way to achieve the objectives of the organization<sup>10</sup>.

As per International Organization for Standardization standard ISO 8402:1994, it is a management approach of an organization centered on quality, based on the participation of all its members and aiming at long term success through customer satisfaction and benefits to all members of the organization and society<sup>11</sup>.

As per The American Society for Quality, this term was first used to describe a management approach to quality improvement. Simply, it is a management approach to long-term success through customer satisfaction. TQM is based on all members of an organization participating in improving processes, products, services and the culture in which they work<sup>9</sup>.

**REQUIREMENTS FOR IMPLEMENTATION OF TQM<sup>12, 13</sup>**

1. Support from management
2. Employee Training and motivation
3. Thorough knowledge about cause and effects of the process

**TQM: A multifaceted approach**

TQM is a multifaceted approach used for quality management among various branches of pharmaceutical industry i.e. research and development, production and marketing. Various facets of TQM approach are shown in Figure 2.

1. **Research and development:** TQM also plays very vital role in quality management of research and development process. It involves following points:

a. **GLP:** It is also called as ‘Good Laboratory Practices’. It involves strict control over use of animals in the laboratory for experimentation. TQM in GLP involves following points:

- Preparation of protocol or master schedule sheet for the study,

- Maintenance of copy of protocol in the laboratory in which study is to be carried out,
- Periodic inspection of facility in which study is to be carried out,
- If any change in approved protocol of the study then there should be documentation and approval of the change along with the reason for carrying out the change, and
- Documentation



**Fig. 2:** Various facets of TQM approaches

- b. **GCP:** It is also called as ‘Good Clinical Practices’. It involves strict control over use of human beings in clinical trials. The regulations for GCP are almost similar to that of GLP. The major difference being that before starting study or involving any subject or human being into the clinical trials. A complete duly filled informed consent form should be taken from subjects along with their signature to make sure that subject is known he/she is involved in clinical trials. These records should be maintained. If patient dropout involve during the study then number of dropouts along with reason of dropout from study should be documented.
2. **Manufacturing:** In production, which include manufacturing of both raw materials and API, along with production and packaging of dosage form.
3. **Post marketing surveillance:** It also includes quality management based on market survey i.e. based on post marketing surveillance and involves change control and its documentation if any change is required in the approved process.

**Approaches for TQM**

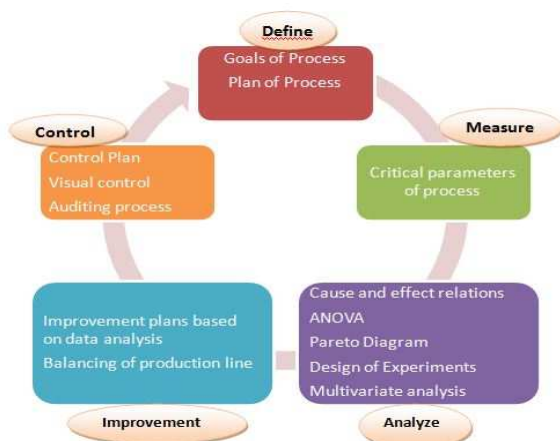
Various approaches as practiced by industries in TQM of pharmaceutical process are:

**Six Sigma Technique**

These are set of tools or techniques used for process improvement or quality management of process. Six Sigma technique can improve the quality of process outputs by identifying and removing the causes of defects (errors) and minimizing variability in manufacturing and business processes<sup>14-16</sup>.

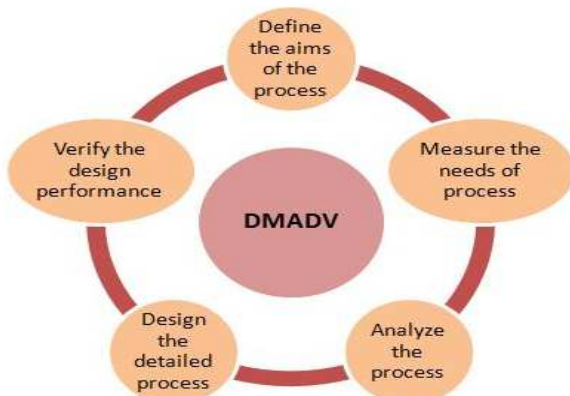
Six Sigma involves two methods:-

1. **DMAIC:** It is an abbreviation used for an improvement cycle, which involves 5 Phases. It is used generally for improving existing business processes. The phases involved are shown in Figure 3.



**Fig. 3:** Various phases of improvement cycle

2. **DMADV:** It is used for creating new business processes or creating a new product. It is an abbreviation used for development cycle, which involves 5 Phases. The phases involved are shown in Figure 4.



**Fig. 4:** Various phases involved in creating new business

**Lean manufacturing**

John Krafcik first coined this term in 1988<sup>17</sup>. Lean manufacturing do not include many tools, but it mainly includes reduction of three types of waste:-

- *Muda*- Non-value-adding work,
- *Muri*- Overburden, and

- *Mura*- Unevenness<sup>18</sup>

The main aim of this approach is to minimize the use of those resources, which do not add up to the value of final product which ultimately reduce cost and increase quality<sup>19</sup>. Word lean in the lean manufacturing means putting the right things in right place so that process can go on smoothly without any problem and this will also minimize the production of waste during the process<sup>20</sup>.

**Quality Risk Management (QRM)**

Quality risk management' is defined as a method for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product through the product lifecycle where decisions can occur at any point in the process. It is a widely used management tool used in pharmaceutical industry, which involves systematic procedure for identification, analysis and control of risk involved in any ongoing process in the industry<sup>21,22</sup>. Various parts included in quality risk management are shown in Figure 5.



**Fig. 5:** Parts involved in quality risk management

**Quality risk management includes:**

- **Identification of risks:** It involves identification of risks before they become serious to be solved.
- **Analysis of data:** It involves analysis of risk data that and classifying the risks based on their impact and priority.
- **Planning:** Based on analysis of risk data planning for mitigation of risks involved and making decisions how to mitigate risks.
- **Track:** Monitor the plans for risk mitigation and also monitoring risk indicators.
- **Control:** It involves strict control over risk mitigation plan to avoid deviation from these plans.
- **Communication:** It involves communication of feedback about quality risk management plans,

their usefulness in mitigation of risks and about finding the emerging risks.

#### **Quality by Design (QbD)**

This concept was first given by Joseph M. Juran. He said that quality can be built in product by planning<sup>23</sup>. This technique is used for optimization of composition of ingredients of a formulation by use of statistical method. These statistical methods used for formulation optimization are approved by US FDA. ICH Q8 defines that pharmaceutical Quality by Design (QbD) is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." Pharmaceutical QbD is a systematic, scientific, risk-based, approach to pharmaceutical development that begins with predefined objectives ICH Q8 defines design space from the concept that quality cannot be tested into product but has to be built in by design<sup>24</sup>.

QbD approach requires thorough understanding of product and ongoing process i.e. complete knowledge about critical process parameters and critical quality attributes. It involves design of experiments, which involves identification of critical quality attributes and process parameters. It determines the relationship between critical quality attributes and process parameters in a design space. It designs a control strategy to produce the product consistently. It involves control over these parameters to achieve desired quality<sup>25, 26</sup>.

#### **ISO Series**

ISO 9000 series is a series of standards developed by International organization for Standardization in 1987 to maintain an effective system for quality assurance and quality management of manufacturing industries<sup>27, 28</sup>. In this, ISO 9000 is concerned with the design and implementation of an organization's quality management system is influenced by: its business environment, changes in that environment, or risks associated with that environment; its varying needs; its particular objectives; the products it provides; the processes it employs; its size and organizational structure. It is not the intent of this International Standard to imply uniformity in the structure of quality management systems or uniformity of documentation<sup>29, 30</sup>.

#### **Current Good Manufacturing Practices (cGMP)**

This is also a technique of quality management of pharmaceuticals. Various agencies have given guidelines for good manufacturing practices such as US FDA, WHO, European medicines agency schedule M in India. These include guidance about choosing location,

facilities, clothing, disposal system, sanitation, testing, recording of analysis, recording any reprocessing or recall, filing of change controls if any change in the process. So it is necessary to have thorough knowledge about good manufacturing practices involved in the process to ensure good quality in the product<sup>31-34</sup>.

#### **International Conference on Harmonization (ICH)**

ICH has drafted guidelines for quality risk management of pharmaceutical products as Q9 guidelines and for pharmaceutical product development as Q8 (R2)<sup>22, 24</sup>. Q9 guidelines involve guidance about risk assessment, risk control and also give guidance about various methods for quality risk management such as 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.

So these various approaches such as six sigma, lean manufacturing, quality risk management, quality by design, ISO, cGMP, ICH etc. are used to for TQM of the process. The main tool of TQM is strong and proper system for documentation as any quality management system is incomplete without proper or complete documentation. Because it is common quote that 'anything that is not documented or recorded means not done'<sup>35</sup>. Therefore, for complete implementation of TQM, it is essential that everything should be properly documented in a good readable format that can be easily understood. Specifically if there is any change in the process or any deviation in the process than a proper change control or deviation control should be filed and approved for every change or deviation from the validated procedure.

#### **Recent Technological Advancements Supporting TQM Automated approaches for real time quality management of pharmaceuticals**

Various automated approaches are used in many industries for maintaining quality at different stages of a process. These are part of TQM approach as these automated approaches decrease requirement of sampling and testing at various stages as these analyzers and probes gave automatic reading at every operation and give information on computer that ongoing process is under control or not so help in increase productivity by decreasing in process sampling and testing<sup>36</sup>. Few of such automated techniques for real time quality management are given below:

#### **Brimrose AOTF Multiplexed Analyser**

Brimrose's rugged and high performance on-line AOTF NIR process spectrometers deliver fast-responding and multi-component analysis for a variety of process applications throughout the pharmaceutical, food &

dairy, chemical, polymer, petrochemicals, agricultural, pulp & paper, wine industries and military. AOTF is an optical device that is based upon the acoustic diffraction of light in an-isotropic medium. Near Infrared Spectroscopy (NIR) is currently being used as a quantitative tool, which relies on chemometrics to develop calibrations. The AOTF technology enables these spectrometers to scan very fast and without using moving parts. This makes it the ideal tool for real-time, on-line industrial process control. These analyzers meet all requirements and standards for on-line applications in and are built to work reliably even in long term harsh production environments<sup>37</sup>. This technology has following advantages over conventional methods:

- Rugged, compact device
- No moving parts, Immune to vibrations
- High signal-to-noise ratio
- Work even in harsh environmental conditions

#### **Diffuse reflectance measurement**

It is an excellent sampling tool for powdered or crystalline materials in the mid-IR and NIR (near-infrared) spectral ranges. They can be used for monitor an ongoing process or ongoing reaction<sup>38,39</sup>.

#### **CIP and WIP probes**

CIP is also called clean in place. It involves cleaning of equipment with minimum involvement of the operator. WIP is also known as wash in place. CIP and WIP probes are the probes which monitor this process of cleaning in place and washing in place<sup>40</sup>. Some benefits of CIP and WIP probes are as follows:

- Procedures can be validated,
- Results are reproducible, repeatable and controllable,
- Reduction of cleaning time
- Automatic cycles which ensure every item is cleaned properly every time,
- Reduction of chemical handling,
- Saving of cost including chemicals, water and effluent, labour time etc.,
- Improved health and safety,
- Batch traceability and records, and
- Possibility to use stronger chemicals and higher temperatures etc.

#### **Sensors based technology in packaging**

Sensors based technology in packaging of pharmaceuticals has opened a new vista in online and in-process monitoring of packaging process. Some of the recently used sensors are detailed below:

##### **Ultrasonic sensor for filling level measurement**

These sensors are used to measure filling level in the process. These are the sensors which survive at high temperatures and high pressure. But sensitivity of these

sensors changes with temperature as because speed of ultrasonic waves also changes with change in temperature. So temperature sensing systems should be included in design of system for adjustment of speed of ultrasonic waves<sup>41</sup>.

##### **Fibre optic sensors for presence of product in packing**

It consists of an amplifier and a fiber optic cable. These sensors sense the presence of product in the packaging e.g. in tablet packing if any cavity in the pack is empty, then it will give signal that there is absence of product in the cavity. In automated operations, it stops the process if this problem occurs regularly. It is easy to handle and having very high switching frequency<sup>42</sup>.

##### **Miniature background suppression sensor for content monitoring**

These photoelectric sensors are used for many advanced functions such as background suppression, detection of transparent objects, contrast sensors for color mark etc. In this, detection of product is independent of color. It causes sharp background suppression so detect the product in process very precisely. These sensors are also used for web edge monitoring to monitor edge of the packaging material during packaging<sup>43,44</sup>.

##### **Ultrasonic sensor for adhesive strip detection**

These are the ultrasonic sensors, which involves use of ultrasonic waves for detection of adhesive strip present on packing of products. It detects whether the adhesive strip is damaged or remain intact<sup>44</sup>.

##### **Anti-counterfeiting technologies**

Various techniques used in pharmaceutical industries for detection of counterfeit drugs i.e. fake medicines are as follows:

##### **Holographic technique**

It is a technique which provides a simplified means for consumers to analyse the authenticity of a drug. Holograms are generated by the interference patterns obtained through the interaction of laser beams. Currently available security holograms produce 2D-3D designs<sup>45</sup>. Now a days, holograms are widely available in variety of formats such as holographic shrink sleeves, holographic induction cap seals and holographic hot stamping foil to identify the 'right product'<sup>46</sup>.

##### **Radio-frequency identification (RFID)**

It is one of the most promising authentication technology based on an electronic chip that emits radio frequency waves encoded with a specific ID or code<sup>47</sup>. These specialized chip readers are used to capture the code as the products proceed through the supply chain through card readers<sup>48</sup>. The major advantage is that it does not require line of sight. However the main

drawbacks of this technology are high cost, readability, and lack of item-level protection<sup>47</sup>.

#### **Mass encryption technology**

It is a technique to provide a unique digital identity to every product generated by a computer-based encryption engine. Digital encryption is much more secure because it every can be given its own unique code. The encrypted code is denoted with 16-digit alphanumeric code, printed on packaging during manufacture and therefore provides each medicine with the unique identity. A major advantage advantage of this technology is that consumer can simply verify the authenticity of the drug with the help of codes printed on blister pack, or by entering the code online into an internet site or via SMS<sup>47</sup>.

#### **Track-and-Trace authentication**

It is software that allows brand owners to manage their supply chain. Pharmaceutical companies are empowered to track their shipments from the factory to the retail level, by encryption and decryption in the

same way that courier companies track their shipments as they wind through the shipping chain<sup>47</sup>.

#### **CONCLUSION**

TQM is the most effective tool in quality management of pharmaceuticals. It is recommended strictly by many regulatory agencies but still it is not completely implemented in all the industries especially in India. As India is one of the largest exporters of pharmaceutical products across the globe, strict implementation of TQM is need of the hour in Indian context. Despite of extensive advancement in product development for real time online production and packaging monitoring, their limited utilization by majority of industries remains a major area of concern. In view of producing high quality medicines, this article is a plea for global regulating agencies and pharmaceutical industries for stricter enforcement and sincere adoption of TQM practices in industries.

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