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### UNDERSTANDING INDUSTRIAL PRACTICES FOR PHARMACEUTICAL QUALITY MANAGEMENT- I, EXISTING APPROACHES AND GUIDELINES

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#### **ABSTRACT:**

Quality pharmaceuticals have always been a quest for industries worldwide due to serious concern about safety, efficacy and purity. In view of this, regulatory agencies across the globe have implemented various stringent guidelines to ensure production of pharmaceutical products with assured quality. In order to fulfil norms and implement "quality" concept, pharmaceutical industries have applied a number of quality management approaches like total quality management, quality-by-design and six-sigma etc. Despite of these industrial practices, these approaches and guidelines are not clear till date for beginners. The focus of present article is to understand roles of drug regulatory authorities, various steps involved in discovery of a new drug and corresponding guidelines for medicinal product along with to provide an overview of existing approaches for quality management of pharmaceuticals.

**Keywords:** Current Good Manufacturing Practices, Good Distribution Practices, Six Sigma Approach, Total Quality Management, Quality by Design, Quality Management System.

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#### **INTRODUCTION**

A quality management system (QMS) is a collection of business processes focused on achieving desired quality by posing a regulatory policy and quality objectives in terms of requirements of the customer<sup>1</sup>. The adoption of a QMS should be a strategic decision of an organization. The design and implementation of an organization's quality management system is influenced by varying needs, particular objectives, the products provided, the processes employed and the size and structure of the organization<sup>2</sup>. There are a number of principles complementary to requirements for products which are central to the practice of quality management. Design, development and implementation of quality assurance are the most vital function in the pharmaceutical industry. The skills necessary to optimally maintain such a vital function requires additional technical capabilities and competence of the personal that perform such vital functional responsibilities<sup>3</sup>. In pharmaceutical industry, the

"Quality" is a measure of high degree of managerial, scientific and technical disciplines. The control function (Quality control and Quality assurance) deals with acceptance and prevention activities along with this, it also deals with a system of management review of the performance and effectiveness of acceptance and prevention activities<sup>4</sup>. From a public health perspective, the main goal in the pharmaceutical sector is to make readily accessible efficacious, high quality and safe medicines along with other products reported for health claims<sup>5</sup>. In order to achieve, safe, efficacious and quality products, following are the major focus areas:

- Availability of resources (mostly public) needed to cover the costs of medicines and accurate prioritisation of resources to best effect.
- Development and implementation of regulatory guidelines for various aspects of health pharmaceuticals viz. research, production, analysis, quality control and assurance, distribution and use by patient/public.

- Timely updation and strict enforcement of various and regulation through different agencies to meet upcoming challenges.

- Ability to develop new medicines for the many diseases which cannot be satisfactorily treated at the present. In order to control the quality of pharmaceuticals, various regulatory agencies have the responsibilities to regulate all related aspects as give in Table 1.

**Table 1: Pharmaceuticals regulatory agencies across the globe and their responsibilities**

Country	Regulatory agency	Legal responsibility
United States	Food and Drug Administration (FDA)	<ul style="list-style-type: none"> <li>• Protection of public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation.</li> <li>• Advancement in the public health by helping to speed innovations that make medicines more effective, safer, and more affordable.</li> </ul>
India	Central Drug Standard Control Organization (CDSCO)	<ul style="list-style-type: none"> <li>• Regulates standards and regulatory ensures of medicines to promote health and safety of its people.</li> <li>• Provides guidance on health issues and medicines.</li> <li>• Regulate the standards of imported drugs and clinical research in India.</li> </ul>
Italy	Italian Medicines Agency (AIFA)	<ul style="list-style-type: none"> <li>• Promotes good health through medicines by setting pharmaceutical policies and assuring their consistent application nationwide. Promotes pharmaceutical research and development to further the safety and efficiency of drugs and medical devices.</li> </ul>
Argentina	National Administration on Drugs, Foods, and Medical Devices (ANMAT)	<ul style="list-style-type: none"> <li>• Responsible for the oversight and regulation of the pharmaceutical, pharmaceuticals, and Food and beverage industries.</li> </ul>
Bulgaria	Bulgarian Drug Agency (BDA)	<ul style="list-style-type: none"> <li>• Responsible for overseeing the safe production and inspections to laboratories, drugs, and medical devices in order to ensure the quality and safety of drug use.</li> </ul>
China	China Food and Drug Administration (CFDA)	<ul style="list-style-type: none"> <li>• To formulate policies and programs on the administration of drugs, medical devices, health food and cosmetics, as well as food safety at consumption stage.</li> </ul>
Colombia	National Institute of Food and Drug Monitoring (INVIMA)	<ul style="list-style-type: none"> <li>• Ensures the safety and health of the citizens of Colombia.</li> <li>• Ensures the quality and safety of food and drugs that are distributed.</li> <li>• Provides information on drugs and food for consumers and pharmaceutical professionals.</li> </ul>
Denmark	Danish Health and Medicines Authority (DHMA)	<ul style="list-style-type: none"> <li>• Responsible for the oversight and regulation of the pharmaceutical and pharmaceutical Industries.</li> </ul>
Europe	European Medicines Agency	<ul style="list-style-type: none"> <li>• Protects and promotes public health through the evaluation of medicines.</li> <li>• Provides recommendations on the quality and safety of medicines.</li> </ul>
Finland	Finnish Medicines Agency	<ul style="list-style-type: none"> <li>• Promotes the health and safety of the population by regulating medicinal, blood and tissue products, and by developing the pharmaceuticals sector.</li> </ul>
Germany	Federal Institute for Drugs and Medical Devices (BfArM)	<ul style="list-style-type: none"> <li>• Responsible for licensing and registering finished medicinal products as proof of safety and efficacy.</li> <li>• Monitors the risks of medicinal products by collecting and evaluating laboratory reports.</li> <li>• Evaluates and develops safe medical devices in Germany.</li> </ul>
Greece	National Organization for Medicines	<ul style="list-style-type: none"> <li>• Protects public health in relation to medicinal products and medical devices.</li> <li>• Evaluates new safe and effective products, and they control the production of medicines to meet the standards of good manufacturing.</li> <li>• Promotes medical and pharmaceutical research.</li> </ul>
Hong Kong	Department of Health- Drug Office	<ul style="list-style-type: none"> <li>• Responsible for the market surveillance of medicines, risk assessments and complaints of drugs.</li> <li>• Inspects the drugs and licenses manufacturers and retailers.</li> <li>• Conduct research and development for the improvement of drug standards.</li> </ul>
Hungary	National Institute of Pharmacy (NIP)	<ul style="list-style-type: none"> <li>• Licensing authority for medicinal products, and it is also responsible for the authorization of duty-free donations of medicines in and out of Hungary.</li> <li>• Evaluates medicines, issues licenses, and supervises medical testing.</li> </ul>
Iceland	Icelandic Medicines Agency (IMA)	<ul style="list-style-type: none"> <li>• Responsible for assessing the quality and safety of medicinal products in Iceland. Conduct inspections to confirm that regulatory requirements are fulfilled.</li> </ul>
ICH	International Conference on Harmonisation	<ul style="list-style-type: none"> <li>• Brings together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration.</li> <li>• Oversees the standards of drug development and registration.</li> </ul>
Ireland	Irish Medicines Board (IMB)	<ul style="list-style-type: none"> <li>• Protects the public health through regulation of medicines, medical devices, and pharmaceutical products.</li> <li>• Protects public health by testing each medicine and containing all of the necessary data to support its quality, safety, and efficacy.</li> <li>• Conducts inspections at sites of manufacture and distribution of medicines.</li> </ul>
Japan	National Institute of Infectious Diseases (NIID)	<ul style="list-style-type: none"> <li>• Conducts fundamental and applied research on infectious diseases and setting testing standards for the development of antibiotics and vaccines.</li> </ul>
Malaysia	National Pharmaceutical Control Bureau (NPCB)	<ul style="list-style-type: none"> <li>• Ensures the quality and safety of pharmaceutical products.</li> <li>• Testing on drugs to determine quality, and they also evaluate laboratory analyses, research, and information before being produced to the public.</li> </ul>
New Zealand	Medicines and Medical Devices Safety Authority	<ul style="list-style-type: none"> <li>• Accountable for the regulation of therapeutic products in New Zealand. Ensures that medicines meet acceptable standards of safety and quality.</li> <li>• Provide information about medicine to health care professionals and consumers.</li> </ul>
Switzerland	Swiss Agency for Therapeutic Products	<ul style="list-style-type: none"> <li>• Ensures that authorized therapeutic products are of high quality, effective and safe.</li> </ul>
United Kingdom	Medicines and Pharmaceutical Products Regulatory Agency	<ul style="list-style-type: none"> <li>• It regulates by the inspection of manufacturing facility to ensure that companies are complying with regulations or not.</li> </ul>

**PHARMACEUTICAL QUALITY MANAGEMENT - A MULTIDIMENSIONAL APPROACH**

The concept of pharmaceutical quality management system is based on a internationally harmonized guidance ICH Q10, which is developed by the Expert Working Group (Quality) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use. It serves as an effective QMS for the pharmaceutical industry. It enhances the quality of medicines around the world. Pharmaceutical QMS helps to facilitate innovation and continual improvement of pharmaceutical development and manufacturing activities<sup>6</sup>. The parameters taken into consideration for multidimensional approach of pharmaceutical quality management are as follows:

**Pharmaceutical research**

- A) Drug design and discovery
- B) Discovery of new excipients Non- clinical and clinical trials

**Pharmaceutical development**

- A) Manufacturing and development of active pharmaceutical ingredients (APIs).
- B) Manufacture of medical kits and devices for investigation.
- C) Development of drug delivery systems.
- D) Development of medical devises for accurate dosing

**Pharmaceutical manufacturing**

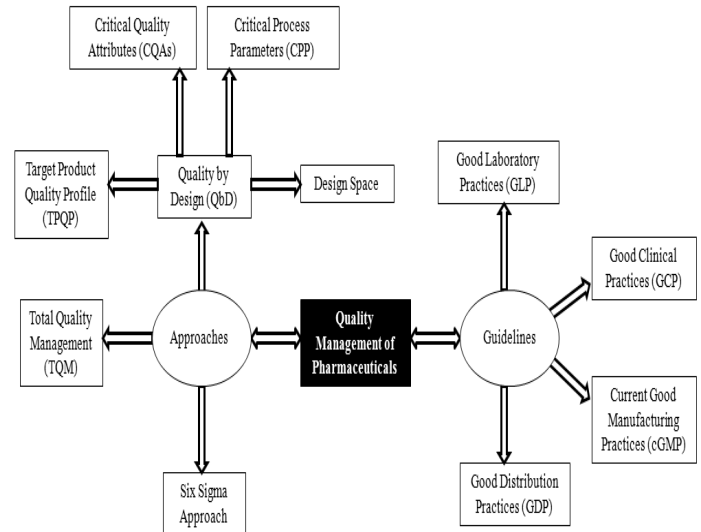
- A) Pilot plant scale-up activities
- B) Manufacturing process of formulation

**Pharmaceutical analysis and quality control**

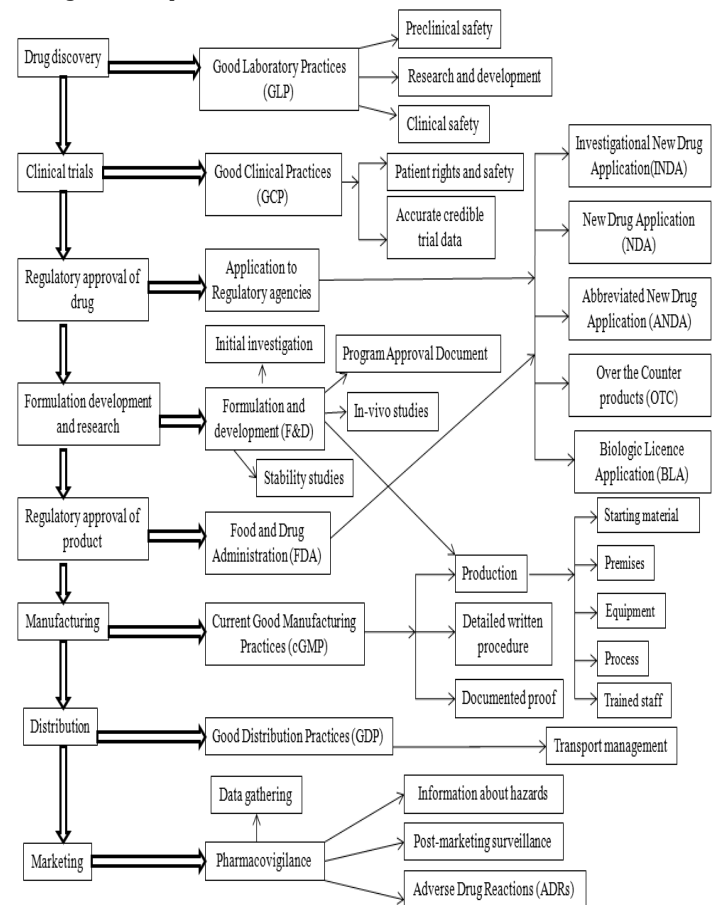
- A) During manufacturing process
  - Acquisition and control of materials
  - Provision of facilities, utilities, and equipment
  - Production (including packaging and labelling)
  - Quality control and assurance
  - Release
  - Storage
- B) During product technology transfer
- C) During product modification discontinuation
  - Retention of sample and related documentation
  - Continued product assessment and reporting
  - Product modification/ rejection
  - Product recall

There are different approaches and regulatory guidelines, which continuously improve the quality of pharmaceuticals by the identification of critical quality attributes and by focusing on customer’s requirements for reproducibility are shown in Fig 1. Various approaches and regulations are implemented by pharmaceutical companies during all the stages of product development and commercialization for

management of desired quality. Involved steps and corresponding quality management tools are represented in Fig. 2.



**Fig. 1:** Various approaches and guidelines for the quality management of pharmaceuticals



**Fig. 2:** Overview of multistep quality management of pharmaceuticals

## CURRENT APPROACHES FOR QUALITY MANAGEMENT OF PHARMACEUTICALS

For the improvement and assurance of quality of the pharmaceuticals, there are some approaches implemented in the pharmaceutical industries for the regulation and maintenance of quality of pharmaceutical products. The main objectives of all these techniques are to establish, implement, and maintain a system that allows the delivery of products with the desired quality attributes. These objectives ultimately contribute to the betterment of quality of finished product as well as better process understanding<sup>7</sup>.

### Total Quality Management (TQM)

TQM is a concept rather than a technique. It is a philosophy that stresses a systematic, integrated, and consistent perspective that would involve everyone and everything in the organization<sup>8</sup>. TQM is an approach of Continuous Quality Improvement (CQI) by focusing on customers' requirements, improving the processes, which relate to these expectations and involving everyone in the process of improvement. TQM is a management philosophy that is devoted to the total customer satisfaction through continuous improvement in the effectiveness and efficiency of the organization and its corresponding processes<sup>9</sup>. The historical evolution of TQM has taken place in four stages:

1. Quality inspection
2. Quality control
3. Quality assurance
4. Total Quality Management

The pursuit of quality being approached through the concept of TQM system is aimed at prevention of defects rather than detection of defects. The concept of total quality control refers to the process to produce a perfect product by a series of measures requiring an organized effort by the entire company to prevent or eliminate errors at every stage in production. Although the responsibilities for assuring product quality belong primarily to quality assurance personnel, it involves many department and disciplines within a pharmaceutical company. To be effective, it must be supported by a team effort. Quality must be built into a pharmaceutical product during product and process design and it is influenced by the physical plant design, space, ventilation, cleanliness and sanitation during routine production<sup>10</sup>.

The assurance of quality of the product depends on more than just proper sampling and adequate testing of various components and finished dosage forms (products). Prime responsibility of maintaining the product quality during production rests with the manufacturing department. Quality assurance personnel

must establish control or check points to monitor the quality of the product as it is processed and up to completion of manufacturing. This begins with raw materials and component testing and includes in-process packaging, labeling and finished product testing as well as batch auditing and stability monitoring<sup>11</sup>. The quality loop showing involvement of various units and necessity of multi- step implementation is shown as Fig. 3. TQM is widely known for improving quality and other performances such as productivity, profit, market share, and competitive edge of organizations of various types.

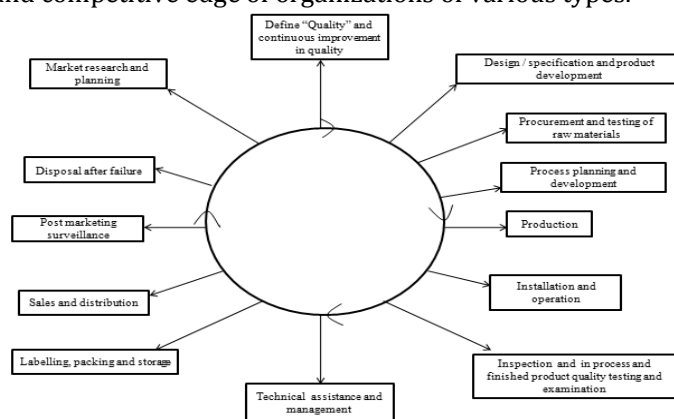


Fig. 3: Quality loop with multistep functionality

### Quality-by-Design (QbD)

Quality is one of the most critical performance measures that can significantly affect a manufacturer's competitiveness<sup>12</sup>. International Conference on Harmonization (ICH) Q8 defines quality as "the suitability of either a drug substance or drug product for its intended use including attributes such as the identity, strength, and purity." ICH Q6A emphasizes the role of specifications stating that "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities"<sup>12,13</sup>.

The concept of QbD was mentioned in the ICH Q8 guidance, which states that "Quality cannot be tested into products, i.e., quality should be built in by design".

QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. It means designing and developing formulations and manufacturing processes to ensure apprehend quality<sup>14</sup>. QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired

characteristics<sup>15</sup>. In order to do this, the relationships between formulation and manufacturing process variables (including drug substance and excipients attributes and process parameters) and product characteristics are established and sources of variability identified. The end goal is more accurate manufacturing processes than those that typically resulted from traditional approaches to drug development<sup>16</sup>. Product quality is ensured by raw material testing, drug substance manufacturing and a fixed drug product quality testing. The quality of raw material including drug substance and excipients is monitored by testing<sup>17</sup>. Main elements involved in QbD approach, as given in Fig. 4, are as follows:

- Defining target product quality profile
- Designing and developing product and manufacturing processes
- Identifying critical quality attributes, process parameters, and sources of variability
- Controlling manufacturing processes to produce consistent quality

A QbD development process may consist of various principles as given below:

- A target product profile describing about use, safety, and efficacy of product.
- Relevant prior knowledge about drug substance, excipients and process operations.
- Designing of formulation and identification and control of critical quality attributes to meet target product quality profile.
- Designing a manufacturing process to produce a final product having selected critical quality attributes.
- Identifying and controlling the critical process parameters and input material attributes to achieve critical quality attributes of the final product<sup>18</sup>.

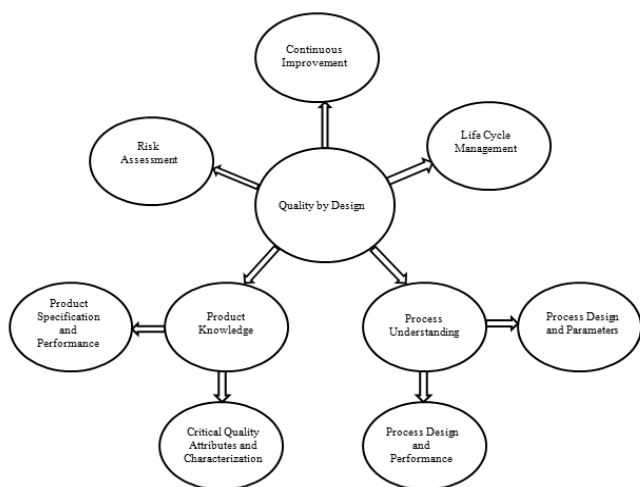


Fig. 4: Development and implementation of Quality by Design approach

#### Factors to be considered for QbD

**Target Product Quality Profile (TPQP):** Food and Drug Administration (FDA) has recently published a guidance defining a Target Product Quality Profile (TPQP). The TPQP provides overall intent of the drug development program, along with information about the drug at a particular time in development. TPQP is organized according to the key sections in the drug labeling and links drug development activities to specific concepts intended for drug inclusion in the drug labeling<sup>18</sup>. The TPQP is a quantitative replacement for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process<sup>19</sup>. The TPQP includes tests such as bioequivalence or stability that are not carried out in batch to batch release<sup>20</sup>. TPQP is related to identity, assay, dosage form, purity, stability in the label. For example, a typical TPQP of a solid oral dosage form would include:

- A. Product characteristics
- B. Identity
- C. Assay and uniformity
- D. Purity/impurity
- E. Stability
- F. Dissolution

The TPQP plays a major role in the drug discovery and development process such as effective optimization of a drug candidate, design of clinical research strategies and constructive communication with regulatory authorities<sup>21</sup>.

**Critical Quality Attributes (CQAs):** ICH Q8 defines CQAs as physical, chemical, biological or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Thus CQA is used to describe both aspects of product performance and determinants of product performance. CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material<sup>22</sup>.

**Critical Process Parameters (CPP):** This can be defined as any measurable input (input material attribute) or output (output material attribute) of a process step, that must be controlled to achieve the desired product quality and process consistency. Parameters have to be considered as CPP if any realistic change in those parameters can cause the product to fail to meet its predefined quality or target product quality<sup>23</sup>. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. The first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between

the maximum and minimum value of interest to the sponsor for each process parameter<sup>24</sup>.

**Design space:** In the presence of interacting CPPs a design space is one approach to ensure product quality although it is not a check-box requirement. The current definition of design space is “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality”<sup>25</sup>. According to ICH Q8, design space defines as “the established range of process parameters that has been demonstrated to provide assurance of quality”<sup>26</sup>.

A design space may be constructed for single unit operation, multiple unit operation for entire process. A design space is way to represent the process understanding that has been established<sup>27</sup>. The benefits of having a design space are clear; one challenge to the effective use of a design space is the cost of establishing<sup>22</sup>. Implementation of these concepts to execute QbD is represented as Fig. 5.

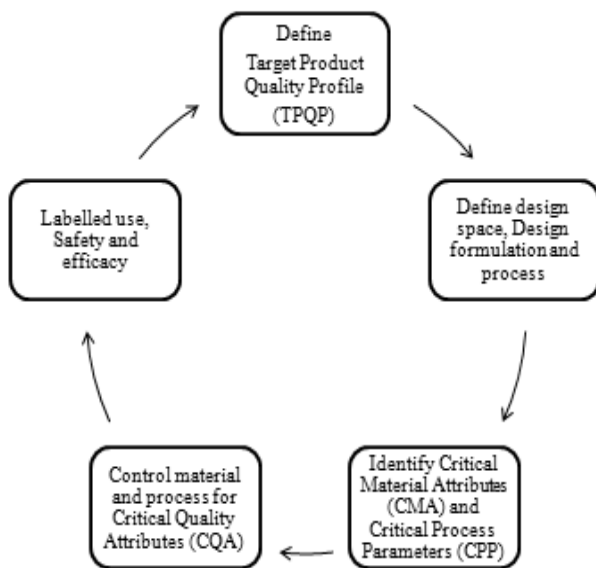


Fig. 5: Implementation of Quality by Design concept

### Six Sigma Quality Improvement Model

Six Sigma approach is a tool use for improvement of methodology and to identify the key sources of variation in a process that may cause defects to occur. In the above said approach, mapping processes are used to measure the output of any process, along with analysis of its input variables; Six Sigma also determines optimizing the output from a process by controlling inputs

The Six Sigma quality improvement refers to the five step process problem solving approach known as DMAIC: (Define, Measure, Analyze, Improve, and Control) as explained below:

- **Define:** This step identifies the expectations of customers are, what the customers want, the process capabilities, and used to project-based improvement efforts.
- **Measure:** This step measures the quality characteristics that reflect possible areas for improvement of customer satisfaction and product performance along with the metrics of data on which the improvement efforts will be based upon.
- **Analyze:** In this step, analysis of previously collected data is to be done with the help of analytical tools such as Pareto analysis as well as process flow diagram, fish-bone diagram, statistical process control charts, for identifying necessary design and process modifications for achieving customer satisfaction and performance objectives.
- **Improve:** In this particular step, resources are allocated so that design and process modifications needed for improvement can be implemented.
- **Control:** In this step, the process is monitored using quality management tools such as Pareto charts and statistical process control charts to ensure that the performance improvements are maintained.

The term “Six Sigma” refers to the level of perfection deliver by a process. Specifically, a “Six Sigma process” allows for six standard deviations between the average performance of the process and its nearest specification limit. This process will produce defects only 3.4 million times per million occurrences (3.4 DPMO) and is regarded for all practical purposes to be “a perfect process”.

Six Sigma approach to process improvement focuses on reducing the variation in the production process to the point where it will be able to meet the specification and tolerance requirement of the product<sup>27</sup>, by improving the process using process statistical tools such as process capability analysis, cause and effect diagram, and statistical process control. Similarly, Six Sigma approach to product design focuses on improving the product design to meet or exceed customers’ satisfaction by using methods such as Quality Function Deployment (QFD), Taguchi’s methods of product design, and robust design<sup>28</sup>.

Six sigma is a tool which measures the level of quality of a system, and to determine the weaknesses; where the organization could do better; and provide better services to the customer<sup>27-29</sup>. Six sigma is a way of instilling in the people in the organization a new perspective on what’s acceptable<sup>29-32</sup>. The major benefit of six sigma is its impact on the bottom line and increased customer satisfaction, higher understanding of solving problems, increased teamwork, and increased employee morale<sup>33</sup>.

## CURRENT REGULATORY GUIDELINES FOR QUALITY ASSURANCE OF PHARMACEUTICALS

### Good Laboratory Practices (GLP)

GLP is defined in the OECD principles as “a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.” The purpose of these principles of GLP is thus to promote the development of quality test data and to provide a managerial tool to ensure a sound approach to the management, including conduct, reporting and archiving, of laboratory studies. These may be considered as a set of criteria to be satisfied as a basis for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions, and the traceability of data. Consequently the principles require institutions to allocate roles and responsibilities in order to improve the operational management of each study and to focus on those aspects of study execution (planning, monitoring, recording, reporting, archiving), which are of special importance for the reconstructability of the whole study. Since all these aspects are of equal importance for compliance with the principles of GLP, there cannot be any possibility of using only a choice of requirements and still claiming GLP compliance<sup>34</sup>.

The GLP principles in their strict, regulatory sense apply only to such studies on pharmaceuticals which are:

- Non-clinical, i.e. are mostly conducted in animals or *in vitro*, and include analytical aspects,
- Conceived to obtain data on the properties and/or safety with respect to human health and/or the environment of the tested substances:
- Intended to be submitted to a national registration authority for the purposes of registering or licensing the tested substance or any product derived from it. In general, and depending on national legal requirements, the GLP requirements for non-clinical laboratory studies conducted for safety evaluation in the field of drug safety testing cover the following classes of studies,
  - Single dose toxicity,
  - Repeated dose toxicity (sub-acute and chronic),
  - Reproductive toxicity (fertility, embryo-foetal toxicity and teratogenicity, peri-/postnatal toxicity),
  - Mutagenic potential,
  - Carcinogenic potential,
  - Toxicokinetics (pharmacokinetic studies, which provide systemic exposure data for the above studies),
  - Pharmacodynamic studies designed to test the potential for adverse effects (safety pharmacology) and

- Local tolerance studies, including phototoxicity, irritation and sensitization studies and testing for suspected addictivity and/or withdrawal effects of drugs.

### Good Clinical Practices (GCP)

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the declaration of Helsinki, and that the clinical trial data are credible. The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). To facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions this guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects<sup>35</sup>.

### Current Good Manufacturing Practices (cGMP)

WHO has issued a primary or fundamental regulation to pharmaceutical industries entitled good manufacturing practice (GMP) for pharmaceuticals. Based on WHO, GMP in many countries have formulated their own requirements for GMP. In USA, as the FDA has a mandate that the marketed drug product be safe effective, the drug product must meet certain criteria for quality and purity. cGMP are to assure the public that the marketed drug product has been properly manufactured and clinically tested respectively. According to FDA regulations, a drug product that does not meet the GMP requirements is considered unacceptable.

A basic of GMP is that “quality must be built into each batch of product during all stages of the manufacturing process, and testing alone can be relied on to ensure product quality”.

This guidance document is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's cGMP regulations (21 CFR parts 210 and 211). The guidance describes a comprehensive quality systems (QS) model, highlighting the model's consistency with the cGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. These guidelines also explain how manufacturers

implementing such quality systems can be in full compliance with parts 210 and 211<sup>36</sup>.

#### **Good Distribution Practices (GDP)**

GDP is a part of quality assurance that ensures the quality of a pharmaceutical product, which is maintained by means of adequate control of the numerous activities which occur during the distribution process as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products.

Distribution holds a significant importance in the integrated supply-chain management of pharmaceutical products. Various people and entities the responsibility is for the handling, storage and distribution of such products, whereas in some cases, a person or entity is only responsible for certain elements of the distribution process. The objective of these guidelines is to ensure the quality and identity of pharmaceutical products during distribution processes. Major thrust areas of this guideline include procurement, purchasing, storage, distribution, transportation, repackaging, relabelling, documentation and record-keeping practices.

The responsibility of storage, sale and distribution of pharmaceutical products are often carried out by various companies, institutions and individuals. This document puts light on various appropriate steps to assist and to ensure the responsibilities involved in the different aspects of the distribution process within the supply chain and to avoid the introduction of counterfeits or substandard products into the marketplace via the faulty distribution chain. In all relevant sections particular role should be distributed amongst various participants as per their applicability which will play a vital role in the distribution of pharmaceutical products.

Major emphasis should be given to following aspects:

- The GDP given guidelines for the distribution of pharmaceutical products, across the globe as per their requirements, as a means of establishing minimum eligibility standards.
- The principles of GDP strongly include both the parameters i.e.
  1. Movement of pharmaceutical products in forward direction in the distribution chain i.e. from manufacturer to dispensing entity afterward to patients.
  2. Movement in backward direction e.g. as a result of the return or recall thereof.
- The principles of GDP include distribution of donated to ensure their quality and efficacy.
- As per GDP guidelines, distribution process includes drug diligence so that procedures related to

traceability and recognition of security risks can be taken into consideration well in time.

- A strong and healthy collaboration between all parties including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of pharmaceutical products to patients should be there to ensure the quality and safety of pharmaceutical products and to prevent the exposure of patients to counterfeit pharmaceutical products<sup>37</sup>.

#### **International Conference on Harmonisation (ICH) Guidelines**

The concept of current pharmaceutical QMS is based on a internationally harmonized guidance ICH Q10, which is developed by the Expert Working Group (Quality) of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use. USFDA shows final phases, for adoption by the regulatory bodies of the European Union, Japan, and the United States, which describes a model for a pharmaceutical quality system that encourages the use of science and risk-based approaches and can be implemented throughout the different stages of a product lifecycle<sup>38-41</sup>. It serves as an effective QMS for the pharmaceutical industry. It integrates the fundamentals of GMP regulations, International Organization for Standardization (ISO) quality concepts, and complements ICH guidelines “Q8 Pharmaceutical Development” and ICH “Q9 Quality Risk Management. It is an additional guidance as part of technical requirements for registration of pharmaceuticals for human use, which is not mandatory in nature. It enhances the quality and availability of medicines around the world. It helps to facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities<sup>42</sup>.

#### **CONCLUSION**

Pharmaceutical industry is supposed to focus on the quality of administrative as well as service function, with some traditional approaches adapted from earlier industrial models along with some modern approaches. This paper has specifically focused on the today's quality management system, which is a tool used in the industry for the management of quality of pharmaceuticals. Pharmaceutical industry is surrounded by most astringently regulated manufacturing units, which plays an ultimate role for management of quality of the finished pharmaceutical products. The implementation and understanding of appropriate quality management system model enables a pharmaceutical organization to



fulfill its ethical as well as regulatory responsibility of including management of identity, quality, safety, purity and efficacy of finished medicinal product, which makes good business sense. Hence techniques which have been applied or need to be applied for the quality management of pharmaceutical products in the industries should be taken into consideration with extra care.

#### REFERENCES

1. Y. Anjaneyulu, and R. Marayya. Quality assurance and quality management in pharmaceutical industry, Pharmamed press, Hyderabad, 2009, pp. 1-7.
2. J. Biolos. Six sigma meets the service economy-six sigma: it's not just for manufacturing, Harv. Manag. Updat. 7: 3-5 (2002).
3. J. M. Caudron, N. Ford, M. Henkens, C. Mace, R. Kiddle-Monroe, and J. Pinel. Substandard medicines in resource-poor settings: a problem that can no longer be ignored, Trop. Med. Int. Health 13 (8):1062-1072 (2008).
4. P. N. Newton. Counterfeit anti-infective drugs, Lancet. Infect. Dis 6(9): 602-613 (2006).
5. E. Wondemagegnehu. Counterfeit and substandard drugs in Myanmar and Viet Nam. Geneva, World Health Organization (1999).
6. N. Dubey, R. Sharma, H. Gupta, N. Dubey, and N. Dubey. Pharmaceutical Quality Management System: Current Concept, J. Adv. Pharm. Edu. Res 1(2):120-124 (2011).
7. G. Isaac, C. S. Rajendran, and R. N. Anantharaman. Significance of quality certification: The case of the software industry in India, Qual. Manage. J. 11 (1): 8-32 (2004).
8. J. P. Corrigan, The art of TQM, Qual. Prog. 28 (7): 61-66 (1995).
9. J. E. Enders. Quality assurance and control. In: Gennaro AR. (Ed.). Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, New York, 200, pp. 980-985.
10. L. Lachman, S. A. Hanna, and K. Lin. Quality control and assurance. In: Lachman. L, Lieberman HA, Kanig JL. (Eds.). The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, Bombay-India, 1976, pp. 804-855.
11. X. Y. Lawrence. US FDA question-based review for generic drugs: A new pharmaceutical quality assessment system, Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector 4(4): 239-246 (2007).
12. P. H. Calcott. How QbD and the FDA Process Validation Guidance Affect Product Development and Operations, Part, BioProcess International 9(10):12-17 (2011).
13. C. S. Kumar, and R. Panneerselvam. Literature review of JIT-KANBAN system. The Int. J. Manuf. Technol. 32(3-4):393-408 (2007).
14. Y. Dallery, and S. B. Gershwin. Manufacturing flow line systems: A review of models and analytical results, Queueing Syst. 12(1-2):3-94 (1992).
15. M. Colledani, and T. Tolio. A decomposition method to support the configuration/ reconfiguration of production systems, CIRP Ann. Manuf. Technol. 54(1): 441-444 (2005).
16. R. A. Lionberger, S. L. Lee, L. Lee, A. Raw, and X. Y. Lawrence. Quality by design: concepts for ANDAs, AAPS J. 10(2):268-276 (2008).
17. S. Jain. Mechanical properties of powders for compaction and tableting: An overview. Pharma. Sci. Technol. Today 2(1):20-31 (1999).
18. World Health Organization. Application of hazard analysis and critical control point (HACCP) methodology to pharmaceuticals (Annex 7), WHO Expert Committee on Specifications for Pharmaceutical Preparations (2003).
19. G. S. Banker, A. Y. Gore, and J. Swarbrick. Water vapour transmission properties of applied polymer films, J. Pharm. Pharmacol. 18 (S1): 205S-211S (1966).
20. F. Boukouvala, F. J. Muzzio, and M. G. Ierapetritou. Design space of pharmaceutical processes using data-driven-based methods, J. Pharm. Innov. 5(3):119-137 (2010).
21. C. Chen. Implementing quality by design: ONDQA initiatives. Advisory Committee for Pharmaceutical Science [online]. 2006 [cited 2014 November 5]; Available from: <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4241s1-index.htm>.
22. R. A. Lionberger, S. L. Lee, L. Lee, A. Raw, and X. Y. Lawrence. Quality by design: concepts for ANDAs, AAPS J. 10(2):268-276 (2008).

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#### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

23. W. P. Ganzer, J. A. Materna, M. B. Mitchell, and L. K.Wall. Current thoughts on critical process parameters and API synthesis [online]. 2005 [cited 2014 November 5]; Available from: <http://www.pharmtech.com/node/239694>.
24. M. H. Safizadeh, L. P. Ritzman, D. Sharma, and C. Wood, An empirical analysis of the product-process matrix, *Manag. Sci.*42 (11): 1576–1591 (1996).
25. E. Davis, and M. Ierapetritou. A kriging based method for the solution of mixed-integer nonlinear programs containing black-box functions, *J. Global Optimiz.* 43(2-3):191-205 (2009).
26. S. Curry, R. Brown. The target product profile as a planning tool in drug discovery research, *Pharmatech.* 67-71 (2003).
27. FDA CDER. Draft guidance for industry. Q8 pharmaceutical development, version 4.3 (draft), Nov, 2004.
28. J. Antony. Six sigma for service processes, *Bus. Process Manag. J.* 12(2): 234-248 (2006).
29. J. Antony, F. J. Antony, M. Kumar, and B. R. Cho. Six sigma in service organizations: Benefits, challenges and difficulties, Common myths, empirical observations and success factors, *Int. J. Qua. Rel. Mgt.* 24(3): 294-311(2007).
30. R. L. Edgeman, D. Bigio, and T. Ferleman. Six sigma and business excellence: strategic and tactical examination of IT service level management at the Office of the Chief Technology Officer of Washington, DC, *Qual. Reliab. Eng. Int.* 21(3): 257-273 (2005).
31. T. N. Goh. A strategic assessment of six sigma, *Qual. Reliab. Eng. Int.* 18(5): 403-410 (2002).
32. G. Wessel, and P. Burcher. Six sigma for small and medium-sized enterprises, *The TQM Magazine* 16(4): 264-272 (2004).
33. T. Chakrabarty, and K. C. Tan. The current state of six sigma application in services, *Managing Service Quality: An International Journal* 17(2):194-208 (2007).
34. World Health Organization. The UNICEF-UNDP-World Bank-WHO Special Programme for research and training in Tropical Diseases-TDR, WHO [online]. 1975 [cited 2014 Apr 4]; Available from: [http://www.who.int/trypanosomiasis\\_african/partners/tdr/en/](http://www.who.int/trypanosomiasis_african/partners/tdr/en/).
35. International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: guideline for good clinical practice E6 (R1), In International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 10 (1996).
36. Food and Drug Administration. CFR-Code of Food Regulations Title 2, Parts 210 and 211, FDA [online]. 1996 [cited 2014 Apr 4]; Available from: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210>  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211>.
37. World Health Organization. Good distribution practices (GDP) for pharmaceutical products, WHO [online]. 2005 [cited 2014 Apr 4]; Available from: [http://www.who.int/medicines/services/exportcommittees/pharmprep/QAS\\_068Rev2\\_GDPdraft.pdf](http://www.who.int/medicines/services/exportcommittees/pharmprep/QAS_068Rev2_GDPdraft.pdf)
38. World Health Organization, WHO Technical Report Series, No. 957, Annex 5, WHO good distribution practices for pharmaceutical products. 235- 264 (2010).
39. Q10 Pharmaceutical Quality System, U.S. Department of Health and Human Services Food and Drug Administration Centre for Drug Evaluation and Research (CDER) Centre for Biologics Evaluation and Research(CBER), p. 2-19, 2009.
40. L. Lakhali, F. Pasin, M. Limam. Quality management practices and their impact on performance. *Int. J. Qua. Rel. Mgt.* 23(6): 625-646 (2006).
41. A. Moy, EMEA and FDA approaches on the ICH Q10 on pharmaceutical quality system, *Pharma Times* 41(8) :15-18, 2009.
42. International Conference on Harmonisation Working Group [website] [cited 2014 Apr 4]; Available from: <http://www.ich.org/home.html>.