AN OVERVIEW ON INTERRELATIONSHIP BETWEEN QUALITY BY DESIGN (QbD) & SIX SIGMA

Kapil Joshi*, Abhay Asthana, Subhash Pande, Gyati Shilakari Asthana, Kishan Singh and Garima Goomber

1Dr. Reddy’s Laboratories Ltd, Village Mauja Thana, Baddi-Solan, 173205, Himachal Pradesh, India.
2Pharmaceutics Research Lab, M.M. College of Pharmacy, M.M. University, Mullana-Ambala, 133207, Haryana, India.
3Zydus Cadila Healthcare Ltd, Moraiya, Sanand, 382110, Gujarat, India.

ABSTRACT

Quality is primary attribute to any industry and its products manufactured. Quality by design (QbD) and six sigma is the modern approach for pharmaceutical quality development and management. This paper gives an idea about the interrelationship between pharmaceutical QbD and six sigma and describes the use of both (QbD and six sigma) to ensure the quality of pharmaceuticals. The use of QbD and six sigma principles (using DMAIC and DMADV) during product development provide opportunities to facilitate innovation and continual improvement throughout the product lifecycle which can increase the efficiency of manufacturing processes; reduce the defects and product non-compliance, resulting in cost savings for pharmaceutical companies. QbD and six sigma can also be helpful for the use of innovative technologies and enhance the use of new approaches to perform process validation like continuous process verification. QbD is a systematic approach and has the potential to make a positive contribution towards drug development and six sigma is a project oriented, statistical approach for reducing variability, removing defects and eliminating waste from products and processes.

KEY WORDS: Quality by Design, Six sigma, Critical Quality Attributes (CQAs), DMAIC (Define, Measure, Analyze, Improve, Control), DMADV (Define, Measure, Analyze, Design, Verify).
INTRODUCTION
The Pharmaceutical industry works hard to develop, manufacture and bring new medicine to the market and to comply with regulatory requirements so that the formulations produced will be safe, effective and meet patient’s requirements. Now a days, continuous quality improvement has become an important business strategy for pharmaceutical industry. Quality is a competitive tool that can result in considerable advantage to patient as well as the organization. In order to produce safe and effective medicine and to meet regulatory requirements, quality should be achieved at every stage of production. Continuous changes in any formulation and manufacturing processes during development and life cycle management should be looked upon as opportunities for drug product development and which further supports establishment of ultimate quality in the product. The product should be designed to meet patient’s needs with the intended quality and performance. There are various approaches used for product development and quality management such as QbD and Six Sigma approach. QbD is a systematic approach towards product development, whereas six sigma is a statistical approach used for pharmaceutical quality management and continuous product improvement. QbD is essential to assure pharmaceutical quality by understanding and controlling formulation and manufacturing variables. On the other hand, with the help of disciplined, project oriented, statistically based Six sigma approach, the variability, defects and wastes from the products and processes can be reduced. The objective of present article is to discuss the concept of interrelationship between pharmaceutical QbD approach and six sigma technology by describing their major components, concluding how these both together can be helpful to explore the processes or techniques for continual improvement during life cycle of product, which ultimately provide a high quality product to the market.

QUALITY BY DESIGN (QbD)
The concept of QbD was mentioned in the ICH Q8 guidelines, which states that, “Quality should be built in by design and cannot be tested into products.”
Acc. to ICH Q8 (R2), QbD is defined as-
“A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control which is based on sound science and quality risk management.”

Acc. to FDA PAT guidelines, Sep.2004, QbD is defined as-
“A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in process materials and processes with the goal of ensuring final product safety.”

**Origin of QbD**

The QbD approach was relatively new to the pharmaceutical industry at beginning of 21st century. During 21st century, the regulatory agencies like FDA (Food and Drug Administration) and other have embraced a new paradigm for regulation of pharmaceuticals in order to make significant improvement in manufacturing technology. In mid-2002, U.S. FDA published a concept paper on current GMP for 21st century and this concept was QbD which expresses that industry should built safety, quality and efficacy in products. QbD came into effect in big way with the advent of the FDA CMC (Chemistry, Manufacturing and Controls) pilot program and submitted regulatory filing based on a QbD framework. These help the industry and regulators to look towards QbD.

---

**Fig. 1 - Foundations of QbD**

**Regulatory Guidelines for Pharmaceutical Product Quality and QbD**

“Fig. 1” shows ICH guidelines providing significant relevant documents as ICH Q8, (Pharmaceutical Development), ICH Q9 (Quality risk management) and ICH Q10 (Pharmaceutical quality systems) that describes usage of quality by design to ensure drug
product quality. ICH Q8, Q9 and Q10 are the main regulatory guidelines for implementation of QbD that provide tools and elements of QbD for Quality risk management and provide various regulatory perspectives for continuous improvement during product lifecycle respectively.\(^{[1, 4, 8, 9]}\)

**Elements of QbD\(^{[3, 4, 10]}\)**

The ICH Q8 (R2): Pharmaceutical development describes the various elements of quality by design which are - Quality Target Product Profile (QTPP), Identifying CQA’s, Risk assessment, Design product, Defining Product Design Space, Control Strategy, Lifecycle management and continuous improvement.

**Advantages of QbD process**

1) QbD improves development capability by performing development work in a more effective and rationalized way.

2) It provides opportunities for developing more reliable, robust processes and products, improves control strategy and increases process capability.

3) QbD allows continuous improvement of manufacturing processes using control strategies throughout the product lifecycle with reduced need for post approval changes.\(^{[11, 12, 13]}\)

**SIX SIGMA**

**Definition**

Six sigma has 3 distinct elements to its definition which are:

Measure: - a statistical description of how far a process deviates from perfection.

Target: - 3.4 defects per million opportunities.

Philosophy: - a consistent business strategy focused on reduction of cost through the reduction of variability in products and processes.\(^{[6, 14, 15]}\)

“Six sigma is a statistical concept or a quality management approach that measures a process or a product in terms of defect at six sigma level having 3.4 defects per million opportunities and offers a way to focus on developing and delivering near to perfect product and services.”\(^{[6, 16, 17]}\)

In statistics, six sigma is defined as having 3.4 defects per million opportunities (DPMO) where the term sigma is used to represent the variation about the process average or a success rate of 99.9997%. If an organization is operating at 3 sigma level for quality control, that means attaining the success rate of about 93% or 66,800 defects per million opportunities.
DPMO = DPU*1000, 000 / Opportunities for error.
Where; DPU (defects per unit) = no. of defects discovered / no. of units produced.[18, 19]

**Historical development of six sigma**
The roots of six sigma as a measurement standard can be traced back to Carl Frederick Gauss (1777-1855) who introduced the concept of normal curve. Six sigma as a measurement standard in product variation can be traced back to 1920s when Walter Shewhart described that a process requires correction at a point of three sigma from the mean. [18, 19, 20] Two years ago; cross-functional continuous improvement teams involving quality assurance, engineering and operational, at Westborough, Massachusetts applied DMAIC principles to solve a major capacity problem for a key product. [20, 21]

**Six sigma methodology**
Six sigma methodology aims to implement a measurement based strategy that focuses on process improvement and variation reduction which is accomplished through the use of following two six sigma methodologies:
1) DMAIC i.e. Define, Measure, Analyze, Improve, Control
2) DMADV i.e. Define, Measure, Analyze, Design, Verify.

1) **Managing process improvement projects**
The six sigma methodology used for managing existing process and product improvement is a five step DMAIC methodology which provides reduction of defects and increases system availability. [6, 14, 22]

2) **Managing new development projects**
The DMADV is a methodology used for managing six sigma projects that helps in new product or system development such as developing a new industrial product. [14, 17, 22]

**Advantages**
Six sigma is used to enhance the product improvement in both manufacturing and marketing in pharmaceutical industry. [6] Six sigma methodologies helps to measure the customer benefits by improving the quality of products, price reduction, improving the delivery times to market, and by increasing financial support to new development projects. Six sigma principles are very important for healthcare sector because of the healthcare nature of zero tolerance to mistakes and potential for reducing medical errors. [15, 18, 19, 21]
Table 1: Sigma levels and their relative impact on process performance.[6,14,21]

<table>
<thead>
<tr>
<th>Sigma performance levels</th>
<th>Defects per million opportunities(DPMO)</th>
<th>Product Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 sigma</td>
<td>308,537</td>
<td>69.2%</td>
</tr>
<tr>
<td>3 sigma</td>
<td>66,807</td>
<td>93.3%</td>
</tr>
<tr>
<td>4 sigma</td>
<td>6,210</td>
<td>99.4%</td>
</tr>
<tr>
<td>5 sigma</td>
<td>233</td>
<td>99.977%</td>
</tr>
<tr>
<td>6 sigma</td>
<td>3.4</td>
<td>99.999966%</td>
</tr>
</tbody>
</table>

Table 1. Represents the various sigma levels and their relative Defects per million opportunities (DPMOs) with their impact on final product yield.

INTERRELATIONSHIP BETWEEN SIX SIGMA & QbD

In pharmaceutical industry, QbD is a proactive approach used for designing and developing formulations and manufacturing processes to ensure predefined product quality whereas six sigma methodology is systematic data driven approach to problem solving with the help of statistical tools and analysis, to have a good quality product for the customers.[12, 14] Both QbD and Six sigma are interrelated with each other as follows:

A) Various quality systems are used to maintain adequate control and to assure the control of product quality like: 1) Change control 2) Validation 3) Trending and Analysis 4) Quality risk management 5) Product improvement program.[3, 23]

These quality systems help the pharmaceutical companies to improve the product quality, improve cGMP compliance and facilitate continuous improvement. Validation is a necessary part of quality system, it is an ongoing program used for assurance of quality and process optimization and to increase output. Acc. to USFDA, “Process validation can be defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product”. [24] The main goal of pharmaceutical validation is to build in quality, safety and efficacy into the product and validate each critical step of manufacturing processes so that the processes must be under control to maximize the probability. [7] Process Validation involves a series of activities taking place over the life cycle of product and process which are classified into 3 stages.[24, 25]

Stage 1 (Process design)

Process design involves defining the commercial manufacturing process based on knowledge gained through development and scale up activities.[7, 24]
Stage 2 (Process qualification)
This stage involves evaluation of process design to determine if the process is capable of reproducible commercial manufacturing.\(^7\),\(^24\),\(^25\)

Stage 3 (Continuous process verification)
This stage involves ongoing assurance of routine manufacturing processes in order to maintain state of control in processes. Data is gathered during this stage with the help of various statistical tools like Six Sigma methodology for detection of variation which suggests ways to improve the process.\(^{24}\),\(^26\) QbD approach comes under the stage 1( Process design) of process validation for designing and developing predefined quality products whereas Six sigma methodology comes under stage 3 i.e. Continuous process verification of process validation uses DMAIC for improvement of processes and products that already exists. The Control phase of DMAIC process applies continuous process verification for maintaining the control of improvements made in process. It means six sigma provides continuous, on-going process and product improvement. Thus both QbD and Six Sigma are the part of Process Validation, and hence they are interrelated to each other.\(^{14}\)

B) There are 2 important approaches used to implement six sigma methodology which are DMAIC and DFSS (also known as DMADV).

Both are used for six sigma implementation but the main objectives of these two techniques are different. DMAIC is a problem solving approach aiming at process improvement. DFSS i.e. Design for Six Sigma is a proactive approach for new product development, process design and prevention of problems by meeting all customer and critical to quality (CTQ) requirements. The major objective of DFSS is “To design the things right at first time”.\(^{22}\) DFSS systematically identifies and optimizes the requirements to ensure that products meets desired characteristics even in the presence of variations and generate the products at six sigma quality level and meet customer’s requirements.\(^{22}\),\(^{23}\) DFSS (DMADV) focuses on preventing problems by designing and developing new product and processes at initial stage as shown in “Fig. 2”.

\(^1\)
Interrelationship of QbD with six sigma is described in “Fig 2”. DFSS is a methodology of six sigma. DFSS is analogous to QbD. Both DFSS and QbD are proactive approach. QbD is also used for designing and developing formulations and processes to achieve predefined product quality. When QbD and six sigma are used in alignment with each other they are known as DFSS which is design for six sigma, hence they are interrelated.  

C) The ICH Q8 (R2) guidance provides examples of possible approaches to achieve enhanced understanding of pharmaceutical products and processes. QbD is a novel approach which is currently being used in pharmaceutical industry that implements quality into the product and manufacturing processes as well as provides continuous process improvement.\(^4, 10\) The step of Life cycle management and continuous improvement under QbD is used for improving the quality of ongoing process and existing products as shown in “Fig. 3”.\(^1, 4, 5\) ICH Q10 guidelines provide details of comprehensive pharmaceutical quality systems that facilitates the use of ICH quality guidelines and continuous improvement in pharmaceutical manufacturing.\(^9\) Continuous improvement is an important element in modern quality system that aims at improving efficiency by optimizing a process and eliminating waste efforts in production. These efforts are mainly directed towards reducing variability in process and product quality characteristics. QbD implements quality into the product and manufacturing processes as well as provides continuous process improvement.\(^2, 7, 9, 13\) Six sigma is an important
methodology used for continuous improvement of products and processes by eliminating defects and wastes. Thus six sigma and QbD both are used for continuous improvement during product lifecycle but in different ways as shown in “Fig. 3”. Thus they are linked to each other.

**Fig. 3 - ICH Q8 (R2): Elements of QbD**

D) QbD approach focuses on robustness, which understands and control the variation. Process robustness is defined as ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at same time.\(^1\), \(^4\) To demonstrate the reproducibility and consistency of process, process capability should be studied. Process capability is a statistical measure of inherent process variability for a given characteristics. It measures that how the process is performing w.r.t. desired outcomes.\(^{26}\) A process is said to be capable if an in-control process is operating within specifications. Process capability measures the uniformity of process. 6σ is the measure of process capability where σ comes from the distribution of product quality characteristics. When the distribution of process characteristics is normal, the natural tolerance limit will be 3σ and the process output will be 99.73%. The process capability indices (Cp, Cpk, Pp, Ppk) provide a common metrics to evaluate the process performance. Cp is the process capability measure, which compares the two sided specification range to the process
width irrespective of where the process is centered. It is the ratio of specification width to
6 × process standard deviation (Cp = USL – LSL/ 6σ). A process is said to be capable if
Cp = 1. [27, 28] QbD is the approach used to improve the process capability and reduce
variability. Six sigma is the most important measure of process capability. Thus both
QbD and six sigma are being used to assess and improve the process capability, hence
they are interrelated to each other. [12, 14, 15]

E) During the product lifecycle, many quality systems are critical in maintaining adequate
control and assure the control of product quality.[4,7] The one of the main quality system is
product improvement programs which covers Six sigma and lean manufacturing, which
provides continuous improvement and assure product’s predefined quality.[15, 17] These
quality systems helps the pharmaceutical companies to : 1) Improve quality of products 2)
Improve cGMP compliance 3) Facilitate continuous improvement 4) Necessitate
implementation of QbD (Q8 - Pharmaceutical development) and Q9 (Quality risk
management). Thus for implementation and effective utilization of QbD; Six sigma as a
product improvement program plays a very important role and thus they are interrelated
to each other. Applying six sigma strategy on established formulations and products is not
simple and may not work. A superior approach is to begin with QbD agenda for a new
product that is targeted to six sigma. QbD “the ultimate control strategy” is the beginning
for six sigma and personnel can monitor the process and maintain control using six sigma
as PAT tool.[1, 2, 13, 14, 20]

APPLICATIONS IN PHARMACEUTICALS [5, 11, 13, 21, 23, 24, 29]
Pharmaceutical industry is the most regulated of all industries. Six sigma and QbD are
contributing
in development of pharmaceutical industry in following ways:-
a) Continuous process and product improvement
b) Customer satisfaction
c) Team building
d) Cost benefits
e) Cycle time reduction

CONCLUSION
As a conclusion we can say that the interrelationship between QbD and six sigma is very
useful and easy to apply for the growth and development of pharmaceutical industry. Based
on this application it can be possible to analyze a lot of processes through many industries, from the design operation to the final product. QbD, Six sigma principles and their tools, play an important role in assistance for higher level of process understanding and offers opportunities for developing control strategies in formulation and process development. QbD and Six sigma serve as a new modern reliable concept. This article reveals the interrelationship between QbD and Six sigma and their potential benefits in pharmaceutical industry when applied together. In such a way, these modern paradigms could stand for essential benefits that leads to development of a quality pharmaceutical product and process with continual improvement throughout the product lifecycle. In many ways the success of companies in the near future may be due to their ability to integrate the concepts of QbD and six sigma.

LIST OF ABBREVIATIONS
QbD: Quality by Design
CQA: Critical quality attributes
CTQ: Critical to quality
ICH: International Conference on Harmonization of Technical Requirements for registration of Pharmaceuticals for Human use
FDA: Food and Drug administration
PAT: Process analytical technology
cGMP: Current Good Manufacturing Practices

REFERENCES
4. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized tripartite Guidelines: Q8 (R2)


