ICIC Express Letters
Part B: Applications
Volume **11**, Number **5**, May **2020**

 ISSN 2185-2766
pp. 501–508

A CASE STUDY ON QBD-6 SIGMA METHOD TO THE PHARMACEUTICAL DEPARTMENT OF L COMPANY

Kang Hee Kim[1] and Sangbok Ree[2,*]

[1]Division of Life Science
LG Chem Ltd.
128 Yeouidae-ro, Youngdeongpu-gu, Seoul 07336, Korea

[2]Department of Industrial Management System Engineering
Seokyeong University
124 Seogyeong-ro, Seongbuk-gu, Seoul 02173, Korea
*Corresponding author: sbree@skuniv.ac.kr

Received November 2019; accepted February 2020

Abstract. *This paper is a case study introducing 6 sigma method to the pharmaceutical development department of L company. L company's pharmaceutical development department operates QbD (Quality by Design) and ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) regulations. QbD production activities consist of product understanding, production process understanding and management. The 6 sigma methodology includes all of QbD production activities. Additionally, 6 sigma retains an educational roadmap and belt system. We proposed a QbD-6 sigma method that combines 6 sigma method with QbD production activity. QbD-6 sigma method is recognized as an excellent technique for improving the productivity and quality of pharmaceutical companies. This technique was first proposed and has had many effects at L company. We expect a QbD-6 sigma method to be applicable to many pharmaceutical departments.*
Keywords: QbD, ICH, 6 sigma, QbD-6 sigma, Pharmaceutical department

1. **Introduction.** In 2013, the United Nations emphasized that the ability of a country's pharmaceutical industry to produce and supply itself without dependence on foreign countries is essential for that country's health rights. With the population aging and the increasing number of chronic and new diseases, the increase in demand for pharmaceuticals is also growing under the growth trend of the world economy.

The global pharmaceutical market has been growing at a CAGR (Compound Annual Growth Rate) of 6% since 2005 and it is expected to continue to expand and to grow by an average of $4 \sim 7\%$ per annum from \$1.1 trillion in 2016, to a market worth up to \$1.43 trillion by 2020. In the US, the operating profit margin of the pharmaceutical industry (23%) is higher than that of automobiles (4.1%), chemicals (8.8%) and semiconductors (18.2%). The pharmaceutical industry is an advanced country-type growth engine that creates high-quality jobs because of its complex industrial characteristics such as biology, microbiology, chemistry, basic science, pharmacy, medicine and statistics [1].

ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) was formed in 1990 by the Association of Medicines in developed countries such as the United States, the European Union and Japan. Due to the different national requirements for drug licensing, pharmaceutical companies are faced with an increasing number of unnecessary costs, which in turn lead to higher drug prices and a delay in supply. The ICH is intended to solve the problems that are disadvantageous to patients. The main role of the ICH is the international coordination of drug licensing

DOI: 10.24507/icicelb.11.05.501

requirements. Pharmaceutical companies must follow the policies required by the ICH in order to develop into a new global pharmaceutical company. Korea became the sixth member country of the ICH in November 2016. L company also produces pharmaceuticals in accordance with the production policies required by the ICH. L company produces 45 kinds of specialty drugs and is one of the top 10 pharmaceutical companies in Korea. Domestic pharmaceutical manufacturers are required to produce products in accordance with the domestic pharmaceutical demand as well as to create added value by becoming a globally competitive exporter.

This study proposes QbD-6 sigma method should be employed as a quality improvement method to improve the efficiency of QbD (Quality by Design) which is the core production process of ICH policies. The QbD-6 sigma method is recognized as an excellent technique for improving the productivity and quality of pharmaceutical companies.

Following the introduction, in Section 2, we reviewed and compared each of QbD and 6 sigma. In Section 3, we proposed the QbD-6 sigma technique and introduced the training process and belt certification system. Section 4 examines the performance of the QbD-6 sigma technique and briefly presents the discussion and application expectations, and in Section 5 conclusion is given.

2. **QbD and 6 sigma.**

2.1. **QbD introduction.** The guidelines of the ICH suggest four things as shown in Table 1. The first Quality Guideline includes drug safety studies, impurity management standards, and flexible drug quality control based on GMP management. The second Efficacy Guideline contains guidelines for the design, implementation, safety and reporting of clinical trials and covers new forms of bio pharmaceuticals, pharmacokinetics, and genomics methods. The third Safety Guideline contains information on carcinogenicity, genotoxicity and regeneration toxicity. The last Multidisciplinary Guideline contains guidelines such as management issues that are difficult to confine to one area.

Table 1. ICH guidelines

Q Quality	Stability study of drug and impurity management standard, flexible pharmaceutical quality control based on GMP risk management
E Efficacy	Guidelines for the design, implementation, safety and reporting of clinical trials
S Safety	Carcinogenicity, genotoxicity, regeneration toxicity
M Multidisciplinary	ICH Medical Terminology, Common Technical Document, Electronics Standards for the Transfer of Regulatory Information

The first Quality Guideline of the ICH consists of Q8 to Q11 regarding the production of pharmaceuticals. Table 2 shows the core contents of Q8, Q9, Q10 and Q11. Q11 is the QbD related guideline.

Q8 requires an understanding of the development and production process of medicines, and confirms the addition of pharmaceutical raw materials and a closed container system, which affects the safety and efficacy of medicines. Q8 defines the concept of starting a QbD goal in advance, systematic pharmaceutical development methods that emphasize understanding of products, processes based on rational science and quality management, as well as process control [2]. Q9 specifies that the proposed approach should be evaluated in terms of the scientific and risk approach described in the permit application [3]. Q10 specifies the Pharmaceutical Quality System [4]. Q11 proposes QbD as a concept for the Development and Manufacturing of Pharmaceutical Substances [5].

Table 2. ICH Q guidance document

Q8 Pharmaceutical Development	Understanding and control of the Design Space
Q9 Quality Risk Management	Understanding and control of Critical Quality Attribute
Q10 Pharmaceutical Quality System	Maintain and control compliance
Q11 Development and Manufacture of Drug Substances	QbD (Quality by Design) relative to Design Space

The QbD suggested by Dr. Joseph M. Juran states that quality can be acquired through a Plan or Design rather than a Test or Control [6]. QbD is an advanced global quality management methodology that anticipates the risks that may arise with the GMP (Good Manufacturing Practice) which uses 21st-century cutting-edge technology.

PAT (Process Analytical Technology) is important in QbD. It can be seen as a prerequisite for Process understanding which is emphasized in QbD. All key variables of the process should be identified and explained, the variables must be controllable by the process, and prediction of product quality characteristics should be accurate and reliable. In PAT, Integrated Analysis includes chemical analysis, physical analysis, microbiological analysis, risk factor analysis and mathematical statistical analysis.

2.2. **QbD step.** The QbD approach runs contrary to the traditional approach of pharmaceutical production. From the viewpoint of the safety and efficacy of patients, the quality characteristics of medicines are determined by selecting the material properties and process variables of the pharmaceutical process, and then finding the optimal conditions through the design of experiments. In the process of finding the quality characteristics for safety and efficacy of the patients, it is necessary to understand the products and processes sequentially, and establishing process control to manage the material characteristics and the process variables in order to develop quality medicine.

1) Product Understanding: At this stage, we describe QTPP (Quality Target Product Profile), derive QA (Quality Attribute) which is a quantitative indicator for assessing QTPP achievement, and select CQA (Critical Quality Attribute) as an important item in QA. CQA are the physical, chemical, biological, and microbiological characteristics that must be within appropriate limits, ranges, and distributions to ensure the quality of the desired product (as defined in Q8).

2) Process Understanding: The final results of this step are CPP (Critical Process Parameter), CMA (Critical Material Attribute) and DS (Design Space). It is a step to figure out the CPP and CMA that have a lot of influence on the CQA, and to derive the DS which is the allowable range of the CPP that does not detract from the quality of the CQA. The process variability associated with CMA and CPP is caused by the quality deviation of the raw materials and the deviation of the manufacturing process of the raw material suppliers. An important factor in the development of pharmaceuticals and the characterization of products and processes is the identification and management of CPPs and CMAs that affect CQA which should be based on statistical evidence.

3) Process Control: In this step, we set up a control strategy for quality control within a specific range of values for the CPPs, which are important variables that affect the CQA defined by the DS. Control strategy is a management plan to ensure process performance and product quality based on product and process understanding. This includes variables, characteristics, facilities, operating conditions, in-process control, final product

specifications, monitoring, management methods, cycles, etc., which are related to the raw materials of the pharmaceutical such as the main ingredients.

The QbD method of management provides a more systematic understanding of where volatility occurs, enhances early stage management, minimizes the need for final product testing, and provides a flexible approach to volatility management. The quality management strategy is constantly updated based on the experience gained throughout the product life-cycle, including the scope of the variables studied and the actual scope of the work.

2.3. **6 sigma method.** 6 sigma is a quality improvement method applied globally since 1990. 6 sigma ensures a high level of quality with only 3.4 defects out of a million. 6 sigma method can be adapted to a company's own culture. In early 2000, 80% of Fortune 100 companies selected 6 sigma as their management innovation. At this present moment, L company's pharmaceutical department has implemented 6 sigma throughout the company [7,8].

6 sigma solves approaches issues by way of the five steps of DMAIC. Step D describes the background from which the task was derived as the define phase, and the rationale for the Project Y (or CTQ: Critical to Quality) selection background to be improved. Step M verifies accuracy of the measurement system of Project Y selected. Present level is measured by Capability Process (CP) or Z value. The current level must be precisely identified before it can be improved. Step A involves finding and analyzing the fatal X among many that may affect Project Y. Step I aims to improve Project Y by optimizing the level of the critical factor X found in Step A. This step utilizes a variety of methods such as an experimental design method. Step C is the control phase, in which a plan to maintain the performance of Project Y is devised by periodically monitoring the fatal X affecting it, and monitoring any changes due to the cause. Once all of the five steps have been completed and the improvement is complete, the best practices are selected and presented upon for reference when performing additional tasks [7,8].

2.4. **QbD and 6 sigma comparison.** Table 3 summarizes the steps of QbD and 6 sigma. The first phase of QbD, the QTPP phase, is similar to the Define phase, which is the first phase of 6 sigma. Y (or CTQ) which is the object of improvement in the 6 sigma methodology correlates with CQA which is in QbD. These are essentially the same concepts. For X that affects Y, all X is called a Potential X in 6 sigma, and the most influential factor is called a vital few X. In QbD, CPP and CMA are searched for in the PP and the MA, respectively. Vital few X and CPP & CMA also refer to the same concepts both of which seek out the optimal condition. In QbD, the best method to find the optimal condition is to use statistical methods; however in 6 sigma method use statistical and other problem solving methods.

6 sigma method is not a fixed methodology that solves problems within a given framework, and it can be applied to all areas with general improvement methods. The biggest

Table 3. QbD and 6 sigma phase

	Product Understanding		Process Understanding		Process Control
QbD	Quality Target Product Profile	Critical Quality Attribute	Critical Process Parameter / Critical Material Attribute	Design Space	Control Strategy
6 sigma	Problem Define Identify CTQ	Measure CTQ Find Potential Variables	Find Vital Few (Core Variables)	Find Optimal Condition of Vital Few	Maintenance Optimal Condition
	Define	Measure	Analyze	Improve	Control

difference between it and other improvement methods is that the 6 sigma offers a specialist education program and a belt certification system. 6 sigma methods can be applied to QbD without any major change and the introduction of a professional training program as well as the belt certification system makes it possible to exceed the goal pursued in QbD.

3. **QbD-6 sigma Proposal.** From late 2017, the pharmaceutical department of L company combined the QbD with the 6 sigma methodology and declared the QbD-6 sigma suitable for the pharmaceutical industry. 6 sigma maintains a stable quality level that is consistent with the GMP directives of the pharmaceutical industry. QbD-6 sigma conducts management activities to improve quality and maintain quality stability. The QbD-6 sigma task may have steps that are skipped or reduced depending on the situation, and some steps can be performed in a more enhanced form. QbD-6 sigma was modified to suit the characteristics of the pharmaceutical industry, which was very well received and has the education that was found to be satisfactory. Lawrence mentioned in 2018 that the introduction of 6 sigma is necessary for pharmaceutical companies, but L company's drug department introduced 6 sigma before that [9].

3.1. **QbD-6 sigma education.** The central benefits of 6 sigma are in its thorough education road map and its belt system. The education road map is linked to the belt system, with the higher the qualification level having more curriculum. Table 4 shows the education of QbD-6 sigma. QbD-6 sigma will conduct the QbD-6 sigma task after completion of the training, which will help all researchers in the new drug development to implement QbD and enhance their performance in connection with the belt system.

Table 4. QbD-6 sigma education contents

Step	QbD-6 sigma GB	QbD-6 sigma BB		QbD-6 sigma MBB
Capability	Junior (Enter $\sim$ 2 years)	Senior ($\sim$ 10 years)		Professional (10 years $\sim$)
Executive Ability	Use basic statistical tools in (QbD) work	Implement problem solving with statistical tools		6 sigma instructor various analytical methods for improvement tasks
Education Module	M1. 6 sigma M2. Basic Statistics Descriptive M3. QbD Concept M4. QbD Product Understanding – QTPP, CQA M5. Hypothesis Estimation	M6. QbD Process Understanding – CPP, CMA – Design Space M7. Correlation M8. Regression M9. DOE QbD Concept Training as Needed	M10. QbD Process Control – CS M11. MSA M12. SPC M13. Capability Analysis	M14. QbD Overview (M3, M4, M6, M10) M15. 6 sigma Overview (M1, M2, M5, M6, M8, M9 and M11, M12, M13) M16. Big Data Analysis
Period	3 days	3 days	2 days	10 days
Amount	300 pages	350 $\sim$ 400 pages	200 $\sim$ 250 pages	1300 $\sim$ 1400 pages

At the start of the QbD-6 sigma is GB (Green Belt) process, where candidates will learn general 6 sigma concepts and basic statistics, and learn QTPP's overall concepts as well as CQA concepts of product understanding. The QbD basic statistics course is comprised of 3 days of collective training. Basic statistics are of paramount importance in QbD-6 sigma GB education.

QbD-6 sigma BB (Black Belt) must be trained in both QbD experimental statistics and QbD management statistics. With regards to QbD experimental statistics, candidates learn about CPP and CMA, which correspond to process understanding of QbD and

the concept of design space. Correlation analysis and regression analysis are learned through particular cases, as are the various DOE methods that help run QbD. The QbD management statistics, on the other hand, includes the control strategy corresponding to the process control stage of QbD, Measurement System Analysis (MSA) as well as Statistical Process Control (SPC), process capability analysis as well as how to present current levels of process statistically. Both courses must be completed to qualify as a QbD-6 sigma BB certification candidate.

3.2. **QbD-6 sigma belt certification.** Table 5 shows the capacity of QbD-6 sigma for belts. QbD-6 sigma GB is a competence to use descriptive statistics and graphical analysis for QbD activities. After completing the QbD-6 sigma GB curriculum, one project is performed, and the QbD-6 sigma GB is certified after the examination.

Table 5. QbD-6 sigma belt capability

Defining QbD-6 sigma Capabilities			+QbD
QbD-6 sigma MBB (Master Black Belt)	Level 5	To learn and apply new methods to help solve problems	QbD education can be implemented and analysis environments can be created.
	Level 4	6 sigma operating systems can be designed and applied.	QbD activities can be coached.
	Level 3	6 sigma training can be provided and can guide improvement tasks.	QbD activities can be initiated.
QbD-6 sigma BB (Black Belt)	Level 2	6 sigma procedures and tools can be used to solve problems.	Understand the overall concept of QbD, and Design Space can be created with help.
QbD-6 sigma GB (Green Belt)	Level 1	Basic tools for data analysis can be utilized.	Utilize basic statistical and graph analysis required for QbD.

QbD-6 sigma GB undertakes the task of utilizing basic statistical tools in the level of work that can be done by new employees in the second year of employment. Activities in the field itself were recognized as a QbD-6 sigma task, reducing the burden and resistance to the QbD-6 sigma task. A QbD-6 sigma BB is a QbD-6 sigma expert who can improve the design space while understanding the overall concept of QbD. A QbD-6 sigma BB has completed the QbD-6 sigma BB training course. After conducting one or more projects, in which a QbD-6 sigma BB checks theoretical and statistical analysis competencies. These are then subjected to practical evaluations to both verify and certify QbD-6 sigma BB competency. If necessary these evaluations can be conducted in parallel with oral evaluations. The primary QbD-6 sigma BB task is usually recognized as that of solving a problem using statistical tools. QbD-6 sigma MBB (Master Black Belt) Level 3 is the ability to improve QbD overall. Level 4 of QbD-6 sigma MBB is an ability to direct QbD activities. QbD-6 sigma MBB Level 5 is an ability to develop and run the analytical environment for QbD execution.

QbD-6 sigma should not place any time constraints on task resolution because it considers the ability of statistical analysis of individuals to be important. The pharmaceutical department has QbD-6 sigma education and this system is centered on QbD. Moreover, the production site has conducted QbD-6 sigma education and task activities centered on GMP.

4. **QbD-6 sigma Results.** L company's pharmaceutical department made the QbD-6 sigma belt qualification a prerequisite for the appointment of a promotion to organizational director. All employees in the pharmaceutical department participated in QbD-6 sigma training. As QbD-6 sigma champions executives show a high level of interest in QbD-6 sigma, by solving important tasks with a top-down approach, reviewing bimonthly QbD-6 sigma tasks on a regular basis, instructing members on task orientation and encouraging their activities, and finally giving QbD-6 sigma GB or BB certifications. MBB has developed and implemented the QbD-6 sigma education system of L company's pharmaceutical department to develop, trained and supported BB and guided the GB tasks of each business site. QbD-6 sigma was well received and has become established without resistance.

L company's pharmaceutical department introduced QbD-6 sigma and 75.6% of the members achieved QbD-6 sigma GB in 2 years (Table 6). By doing QbD-6 sigma over 96 tasks, it has made many improvements such as productivity improvement (10-20%) and quality cost reduction (5-10 million $).

Table 6. QbD-6 sigma belt ratio

	GB Ratio	BB Ratio	Belt Ratio
Team 1	66.9%	9.0%	75.9%
Team 2	67.3%	7.7%	75.0%
Total	67.0%	8.6%	75.6%

The QbD-6 sigma has a dramatic effect, taking advantage of the sophistication of the 6 sigma technique compared to the QbD-only company. In particular, the effect of DOE was great. One example of the company's use of the QbD-6 sigma technique is that design spaces for prescriptions satisfying the quality standard were proposed using experimental design and response surface analysis to check the production cost of the developed drug.

5. **Conclusions.** In 2009, at the time the H1N1 influenza pandemic was terrorizing the whole world, Korea was able to largely avoid this crisis with no major disasters through the use of the technology of its domestic pharmaceutical industry to develop a domestic vaccine. The possession of pharmaceutical sovereignty to develop, produce and supply essential medicines without reliance on other countries is directly linked to the lives and health of the domestic populace [1]. ICH and other regulatory agencies recommend that QbD be applied to new pharmaceutical development, which has become essential to grow into a global pharmaceutical development company.

In this study, QbD-6 sigma was developed by introducing 6 sigma to improve the quality and efficiency of QbD. The newly developed QbD-6 sigma education system and belt system were also suggested. We are confident that QbD-6 sigma will contribute to the shaping of local pharmaceutical companies into new global pharmaceutical development companies, and we hope QbD-6 sigma will be applied to many sites in the future to this end.

Acknowledgment. The authors also gratefully acknowledge the helpful comments and suggestions of the reviewers, which have improved the presentation.

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