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# Role of statistics in quality by design product development for pharmaceutical industry: a review

S. A. Kale[1*], Dr. V. H. Bajaj[2]

[1]Research Scholar, Dept. of Statistics, Dr. B.A.M. University, Aurangabad (MS), INDIA
[2]Professor and Head, Dept. of Statistics, Dr. B.A.M. University, Aurangabad (MS), INDIA

***Corresponding author e-mail:** kalesushil@rediffmail.com

**ABSTRACT**

Pharmaceutical industry is showing a positive approach towards Quality by Design (QbD) for discovery, development, and commercial manufacturing of biopharmaceutical products. Regulatory agencies are providing various guidelines for pharmaceutical industry to build quality, safety and efficacy into their new biopharmaceutical products. Such concept became known as Quality by Design. To assess the Quality by Design (QbD) product development till robust quality manufacturing, several statistical tools may used. This paper outlines the role of statistics in monitoring, evaluation, optimization and improvement of Quality by Design Product Development for Pharmaceutical Industry.

**Keywords:** DOE, QbD, statistical process control

## INTRODUCTION

Quality means fitness for use. Quality has become one of the most important decision factors in the selection among competing products and services. Quality by Design (QbD) is a concept first outlined by quality expert Joseph M. Juran believed that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned [1]. Although Quality by Design concept have been used to advance product and process in every industry and particularly the automotive industry, they have recently been encouraged by the U.S. Food and Drug Administration (FDA) for pharmaceutical industry as a guideline for the transformation of how drugs are discovered, developed, and commercially manufactured. In August 2002, FDA published a concept paper on current Good Manufacturing Practices for the 21st century. FDA's paper discussed that pharmaceutical companies build quality, safety and efficacy into their new biopharmaceutical products as early as possible. This concept became known as Quality by Design. In QbD system, the product is designed to meet patient requirements, the process is designed to consistently meet product critical quality attributes. The impact of formulation components and process parameters on product quality is understood and critical sources of process variability are identified and controlled. The process is continuously monitored and updated to assure consistent quality over time.

Prior to FDA's significant initiative, Quality by Design (QbD) was most misunderstood tool in pharmaceutical industry. FDA's systematic approach by publishing guidance for industry Q8(R2)[2], Pharmaceutical Development, along with Q9[3], Quality Risk Management, and Q10[4] helped pharmaceutical industry to act and implement Quality by Design (QbD). Besides it helped to achieve product quality with low cost, reduce product waste, predict effects of scale up on final product, analyze or understand reasons for manufacturing failures.

To assess the Quality by Design (QbD) product development till robust quality manufacturing, several statistical tools like multivariate analysis, Design of Experiments (DOE), Model Building and Evaluation, Statistical Process Control, Sampling Plans and many more are available. Here we

discussed role of statistical tools like Design of Experiments (DOE) and Statistical Process Control (SPC).

## PRINCIPLE SOURCES OF QUALITY VARIATION

Identification and a clear understanding of possible source of variation(s) is utmost important before applying any statistical tool in an experimental study designed with Quality by Design approach for pharmaceutical product development. These controlled or uncontrolled variations have an impact on the entire process and its outcome. Vince McCurdy discussed the principal sources of quality variation to a process include [5],

- Material attributes (peroxides, water content, impurities);
- Process parameters (temperature, force, speed);
- Equipment design (baffles, agitator type, surface type);
- Measurement system (sample prep, extraction time);
- Environment (relative humidity, temperature, oxygen content);
- Person (operator, analyst).

It is important to note that the total process variation as measured by the variance or standard deviation (σ) of the average batch data is a function of all sources:
σTotal = f (σMaterial + σProcess + σEquipment + σMeasurement + σEnvironment + σPerson)

## DESIGN OF EXPERIMENTS (DOE)

Design of experiments (DOE) or experimental design is an applied statistics deals with planning, conducting, analyzing and interpreting controlled tests to evaluate the factors that control the value of a parameter or group of parameters. DOE is a systematic approach to investigation of a system or process. DOE was developed by Ronald Fisher in England in 1920 and used in agriculture. Melder & Mead (simplex method in the field of response surface) in the early '60s, Box-Hunter (based on ANOVA methods) in the late '70s and Genichi Taguchi (orthogonal designs) in the early '80s made further significant contributions in the field. Discipline that has very broad application across all the natural and social sciences and engineering. DOE is structured, organized method for determining the relationship between factors affecting a process and the response of that process. The application of DOE is useful for optimizing process and determining the design space, including multivariate relationships. The design space is explained as "The multidimensional combination and interaction of input variables that have been demonstrated to provide assurance of quality" [2]. Robert A. Lionberger, Sau Lawrence Lee and *et al* discussed that design space can be constructed by applying design of experiments (DOE) for a single unit operation, multiple unit operations, or for the entire process [6]. However in the development of a design space, the key issue to efficiency is demonstrating or establishing that the unclassified parameters left out of the DOE are truly non-critical interacting. Sandipan Roy highlighted an importance of Design of Experiment (DOE) as structured and organized method to determine the relationship among factors that influence outputs of a process [7]. Although DOE is not new concepts for the development of manufacturing processes, linking the establishment of design space to the relevant CQA is novel. In our view, DOE is a high end statistical tool useful for conducting experimental design in order to achieve quality by design product development.

## STATISTICAL PROCESS CONTROL

SPC was pioneered by Walter A. Shewhart at Bell Laboratories in the early 1920s. Shewhart developed the control chart in 1924 and the concept of a state of statistical control. SPC is applied in order to monitor and control a process. Monitoring and controlling the process ensures that it operates at its full potential. Key tools used in SPC include control charts; a focus on continuous improvement; and the design of experiments. An example of a process where SPC is applied is manufacturing lines. Statistical process control (SPC) in QbD is the application of statistical methods to identify and control the special cause (non-random variation caused by a specific factor) of variation in a process. Process capability is a statistical measure of the inherent process variability for a given characteristic. Process capability is denoted by Cp and Process capability Index is denoted by CpK.
Widely accepted formula for process capability is 6 σ.
Process Capability (Cp) = + 3 standard deviation (total of 6 σ)

Cp refers the variation in a process about the average value, but average of process not often the midpoint so it is useful to have the process capability index that reflects the both variation of process and the location of process variation. Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, defined as follows:

Process Capability Index (CpK)= (Upper limit of specification-lower limit of specification)/6 σ
If the CpK value is significantly greater than one, the process is deemed capable [8].

Vince McCurdy explained that while QbD is most effective when it is employed at a product/process design level, it should also be accomplished in the manufacturing and quality assurance environments [5]. Continuous improvement of a product and process should be employed throughout the lifecycle of a product. Process capability (CpK) is an extremely valuable metric to indicate which CQAs or other PPAs are least robust. CI efforts generally focus on the low CpK attributes.

V. S. Chopra *et al* reviewed that when the process is running within design space then the product will be of predefined quality [9]. Six sigma continuous improvement approaches was used to control the process which have five phases: define, measure, analyze, improve and control. SPC is a critical support to QbD.

In our view SPC is an important tool to monitor, evaluate process variation especially for robust manufacturing for quality product developed using quality by design approach.

## CONCLUSION

Role of Statistical tool like Design of Experiments (DOE) and Statistical Process Control (SPC) is useful for designing, modeling and interpretation of experiments required during pharmaceutical product development. It helps industry to achieve quality product development and its robust manufacturing. Both DOE and SPC are the statistical tools are widely used to identify source of variations and corresponding challenges.

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