BUSINESS SOLUTIONS

White paper

Quality by Design (QBD)

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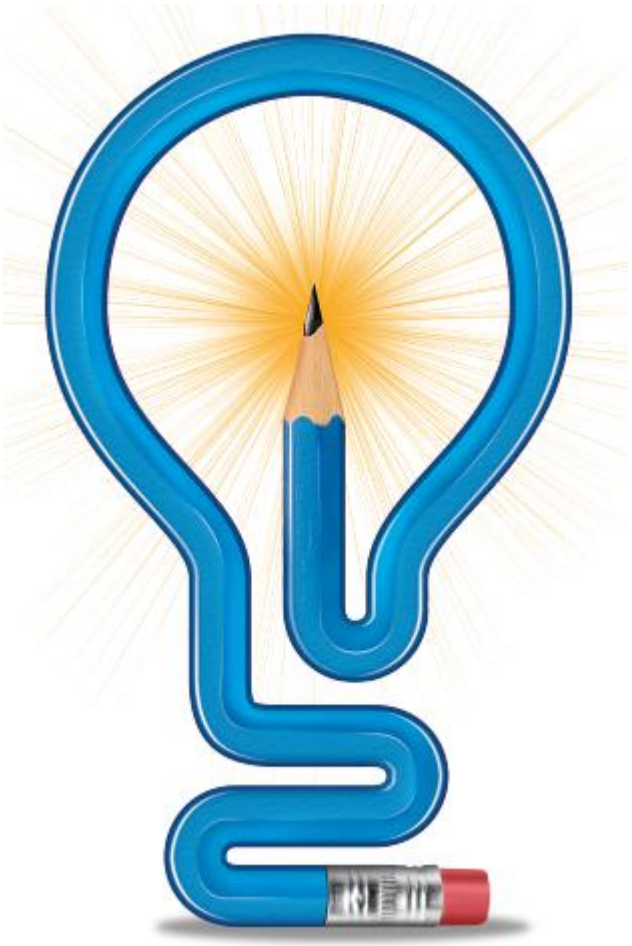

Quality by Design (QbD)

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Introduction

Starting from the 19th century, the pharmaceutical industry has witnessed a major transformation, leading to the innovation of several breakthrough molecules that held the promise of curing several erstwhile incurable diseases. Deeper understanding of human biology, scientific progress and improved manufacturing techniques have all contributed to the intense development and mass manufacturing of numerous drug products. This has also led to an explosive surge in the number of laws and regulations governing drug testing and approvals with a view to safeguard the patient against ill effects that might be associated with process failure.

Events like 'thalidomide tragedy' during 1960s to 1970s, where thalidomide drug was given to pregnant women to cure morning sickness resulted into severe birth defects and it egged regulatory bodies to tighten the quality and safety norms imposed on drug manufacturers. Circa 1990, experts from industry and the regulatory authorities from U.S., Japan, and Europe came together to form the 'International Conference of Harmonization' to bring about harmonization in regulation of pharmaceutical industry across the world. The ICH mooted the idea of Quality by Design in 21st century, which was built around documented quality guidelines.

Today, pharmaceutical industry is a highly regulated industry with the primary aim of protecting patients' safety through imposing regulations pertaining to drug testing and validation. But overregulation has led to a stymieing effect on innovation and also resulted in huge losses due to disparity in current quality levels and desired quality levels. Although the pharmaceutical industry has significantly reduced the death rates, there is still a risk factor linked to the patients, due to shortages of medicine as a result of time taken in testing and drug approval, purity, potency etc.

The aim of FDA and other regulatory agencies therefore has been to bring about a shift in industry paradigm to move away from reliance on testing for quality to building quality into the design of the product and processes. This should in turn bring about a more scientific, technological and risk based approach.

Business Relevance Of Quality By Design

Evolution of Quality

Historically, there have been 3 approaches to quality:

- Quality Control
- Quality Assurance
- Quality Management

Quality Control (QC) is an inspection-based approach. QC is used to assure a certain level of quality in a product or service. Quality Control is a process by which the product quality is compared to the applicable standard. It checks for the non-conformance and checks for defects, when the product is ready. The defects are obviously rejected. The job of the QC Manager is to ensure that the product has the specific attributes and that it meets the predefined standards. Quality control is concerned with examining the product or service — the end result.

Quality Assurance (QA) is more of a preventive measure. Quality Assurance is concerned with examining the process that leads to the end result. Companies use Quality Assurance to ensure that a product is manufactured in the right way, thereby reducing or eliminating potential problems with the quality of the final product. QA establishes and evaluates the processes to produce the products. QA is the responsibility of the entire team and it prevents the introduction of issues or defects.

Quality Management (QM), the latest approach to be adopted by many advanced pharma companies, is an end-to-end approach. It is a new concept not only in pharma but also for a vast majority of industries other than aerospace and automobile. It starts from taking the consumers' requirement into account, gets in to the designing aspect of the product and ends at after-sales feedback. Though traditionally it has been popular in the manufacturing parlance, it has recently started seeping into other industries as well. In the pharma sector, it not just focuses on the drug manufacturing part, but looks at continuous improvements at all levels and aims to reduce the molecule-to-market time which is very high in the pharma world.

Buzz Surrounding Quality by Design (QbD)

Lately 'Quality by Design (QbD)' is generating quite a buzz in the pharmaceutical industry. QbD encompasses design, development, validation and implementation of a robust manufacturing process. QbD means designing and developing APIs/formulations/excipients and manufacturing processes to ensure predefined product quality. "QbD itself is a success story that is evolving. At the same time, we're dealing with globalization, so we really need to push on quality and supply chain issues . . . we should use the highest quality science and technology to ensure that, and we should continue to move away from our traditional methods." Says FDA CDER's Janet Woodcock.

There is strong pressure to develop innovative medicines for unmet medical needs at affordable prices to patients and payers. The pharmaceutical industry is highly regulated by international regulatory agencies that have set very high quality and efficacy conformance standards of medicinal products. There is no doubt that QbD will increase the quality of medicinal products and conserve industry resources.

Many pharma companies have now started engaging with QbD, with numerous projects now underway. Adopting QbD will increase costs at development but this would be offset by more successful launches, less loss in production, fewer deviations, and fewer recalls – so there should be an overall net gain. It applies the concept of 'First Time Right' from the manufacturing industry to the pharma.

Traditional Pharmaceutical Drug Development Approach

Pharmaceutical manufacturing currently relies on processes that are widely seen as inefficient, inflexible and outdated.

In the traditional approach, quality is assured by testing at various stages of manufacturing. First the raw materials are tested, then the processes and then finally the end product. If a particular batch does not conform to the required specifications, the entire batch is rejected as 'Out of Specification'. This leads to an enormous amount of wastage of resources, time and money. Also, any small change in the process requires various permissions from FDA, which in turn is a lengthy process. The product fails to reach the market when there is demand. This in turn leads to shortage in supply and hike in prices. In this approach, the flexibility in the manufacturing process is highly restricted and more emphasis is on the end-product testing.

The following are the probable root causes for the failure of traditional pharmaceutical practices:

▪ The current regulatory review system places little importance on how the design of the manufacturing process can ensure good and reliable product quality.

▪ The research work is done by observing one variable at a time and thus the interactions among the various variables is neglected which plays a significant role in actual process.

▪ Validation efforts start after designing of process is over and ends with surrender after testing. Hence, the discoveries made during validation stage couldn't be implemented in the process.

▪ Product specifications are often derived using test data from one or more batches, but rarely at production scale, and sadly, full mechanistic understanding does not play a large part.

▪ Drug quality is controlled by testing of intermediates and end products. Thus, the quality is tested and not built-in the product.

▪ The time consuming traditional validation process causes delay in the drug release.

▪ The traditional pharmaceutical process is more based on corrective actions taken after problem has occurred rather than taking preventive actions.

From the forgoing discussion, it is evident that the traditional pharmaceutical process will not be able to meet the requirements of 'Risk based modern pharmaceutical approach of 21st century' although it has proved to be satisfactory in fulfilling customer demands in the earlier times when the technology was not that developed. Now, with improving technological advances and need for innovation in pharmaceutical industry, it is necessary for the industry to embrace new approach towards drug development and manufacturing.

What is Quality by Design (QbD)?

Quality by Design (QbD) is at the very heart of modern pharmaceutical development. Quality by Design is a scientific, risk-based holistic and proactive approach to pharmaceutical development with customer (common man) requirements in focus.

QbD approach stands in contrast to the current approach. It places more emphasis on continuous improvement rather than end-product testing. It is a deliberate design effort starting from product conception through commercialization. Quality by Design is build on the basis of customer/patient or a common man's wants and needs and aims to deliver a product, a process or a output that meets those needs.

Quality by Design approach mandates a company to have a sound understanding of their product. QbD makes certain that the product is of predictable and predefined quality. The adoption of QbD includes defining a target product quality profile; designing the manufacturing process from basic principles with a very good understanding of the mechanism involved (good Design of Experiment); identifying critical quality areas, process parameters and potential sources of variability; and finally controlling manufacturing process to achieve the most consistent quality.

Regulatory authorities - both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) - are placing great emphasis on the QbD component as a part of regulatory filing. QbD has become a crucial element of a stream-lined drug development process. QbD-by providing the Quality at the design stage will benefit the organizations by reducing the defects or deviations at the later stages of product development, which prove to be very expensive. It also benefits the organizations on reducing the cycle time for the optimized product development.

A lot of pharma companies are waking up to this and have started taking steps in implementing the same. On the onset, it might look difficult and challenging but its long term payoff is very promising.

SSA's QbD Approach

The following diagram represents the QbD implementation approach:

Step: 1 Identify the Quality target Product Profile of drug

Step: 2 Determine the critical quality attributes

Step: 3 Link the material attributes and process parameter to CQAs

Step: 4 Perform risk assessment

Step: 5 Develop a Design Space

Step: 6 Design and implement control strategy

Step: 7 Manage product life cycle , including continuous improvement

Skills Needed For Best Practices In QbD

SSA Business Solutions has endeavored to bridge the skill gap prevalent in the pharmaceutical industry that has prevented them from successfully embracing QbD. These include, among other things, application knowledge of: Statistics, Risk Assessment, and Design of Experiment. SSA's Workshop on 'Building Blocks of QbD' addresses the following aspects of QbD in significant detail:

- Training provided by experts from the pharmaceutical industry.
- Techniques to identify the Critical Quality attributes of the drug.
- Application of techniques like C&E and FMEA to effectively perform risk assessment and identify the significant process parameters and material attributes.
- Statistical techniques like MSA, ANOVA etc. to effectively carry out DOE.
- Application of DOE with Response Surface Methodology to develop the Design space and optimize it.
- Application of Monte Carlo Simulation to set up the tolerances in the Design space.
- Techniques for effective scale up for manufacturing process.
- Application of Process Analytical Technology to effectively control the manufacturing Process.

Summary

The very nature of the pharmaceutical industry and the direct impact that medicines have on the end users, have raised the need for Quality to be built into the product. The future of pharma industries depends on its ability to innovate and provide effective new drugs in the shortest lead time to the market. The traditional pharmaceutical process is very stringent, bounded and lacks innovation. The traditional approach of drug development is a very time consuming process. The quality that is tested in a traditional way not only leads to heavy losses to the industry but also leads to shortage of drugs in the market. This in turn leads to price hike.

QbD approach takes into account patient/customer needs and emphasizes that Quality should be built into the product. QbD supports development of Design Space under which the process produces drugs of the desired quality. Shifting within the Design Space is not considered as change in QbD approach. It supports PAT for implementing effective control system. QbD believes in continuous improvement and takes proactive actions rather than reactive.

About SSA

SSA is a leading management consultancy firm headquartered in Mumbai, India with local presence in Middle East and Africa and a rich clientele base spread across Asia, Middle East and Africa. SSA provides tailor-made solutions for the various problems faced by an organization with special focus on improving profitability and reducing costs.

SSA in addition to many segments has been consulting many pharma companies as well. SSA has been a pioneer in the field of quality in India and has helped hundreds of organizations imbibe quality in their products and processes worldwide. Taking into account the pressing need of pharmaceutical industry, SSA is offering this program for Implementation of Quality by Design. The program covers all the statistical tools and analytical techniques required for QbD framework. The program features with industry specialists and experts facilitating quality implementation in various industries.

Founded in 1999 with a missionary zeal to make 'Made in India Synonymous to Quality', In well over a decade of its existence, SSA has worked successfully with pharma big weights like Pfizer, Lupin, Novartis, USV Pharma, ACG and many other valued clients DHL, Maruti Suzuki, Reliance Industries, Vodafone, ABN AMRO, Bharat Petroleum, Cadbury, and National Stock Exchange of India, to name a few, and has effected cumulative savings of over US $200 million.

In the area of corporate training, SSA is the first and only institution in India to have been accredited to IACET, USA (International Association for Continuing Education and Training). SSA offers a host of training and certification programs on topics ranging from Lean, Lean Six Sigma to Performance Scorecard.

To know more about SSA, visit us on www.ssa-solutuions.com

Our Clientele