**BP606T. Pharmaceutical Quality Assurance.**

**Unit-One**

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Part– III Hours-01

Quality by design (QbD):

Definition, overview, elements of QbD program, tools

## QbD Overview – a US FDA initiative and its advantages

Since the introduction of Quality-by-Design (QbD) concepts, it has been accepted that quality of pharmaceutical products should be designed and built during the manufacturing process. Most of quality problems are related to the way in which a pharmaceutical product was designed. A poor-designed pharmaceutical product will show poor safety and efficacy, no matter how many tests or analyses have been done to verified its quality. Thus, QbD begins with the recognition that quality will not be improved by merely increasing testing of pharmaceutical products. In other words, quality must be built into the product.

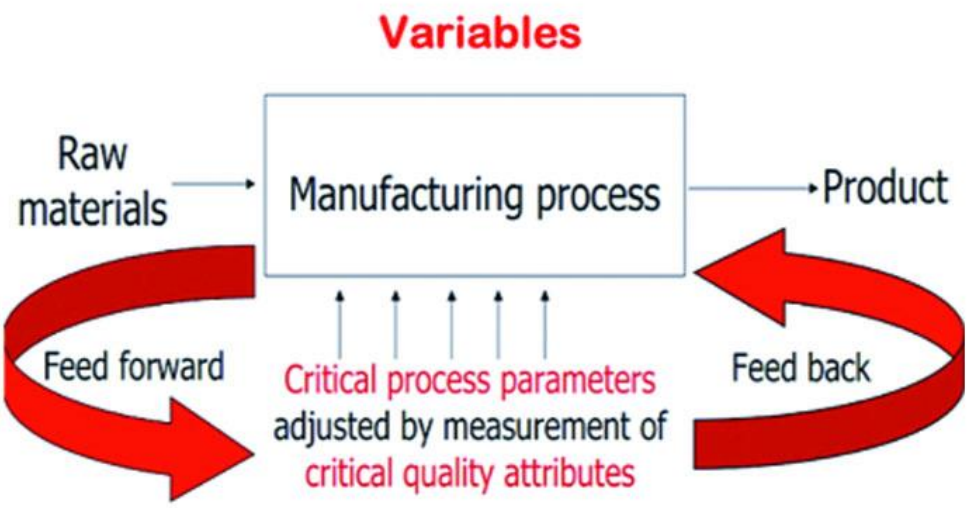


**Diagram-1**

Quality by Design (QbD) is one of the most important initiative by US FDA. "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach in 2002 by FDA was the first step towards this goal of QbD compliance. Same period FDA issued another guideline on "Process Analytical Technology" (PAT) to guide the Generic Industry about the advantages of PAT in Real Time

Release. This was the beginning of the journey towards implementing QbD. The concept is based on enhancement of Process & Product understanding with the help of Risk assessments, identifying Critical Quality Attributes & Critical Process Parameters to be monitored thru right control strategy. Customers are benefitted thru consistency in commercial manufacturing. FDA recommended the implementation since 2013.

Part 1 deals with Understanding of QbD & its benefits to the Generic Industry. Part 2 will deal with detailed step by step implementation of QbD and short Case studies to resolve issues.

**US FDA initiative on QbD:**

QbD principles have been adopted by the US Food and Drug Administration (FDA) for the discovery, development, and manufacture of drugs.

**The FDA initiative is outlined in its report "Pharmaceutical Quality for the 21st Century:** A Risk-Based Approach. FDA has taken this initiative to guide the Pharmaceutical Industry on how to implement the concepts of QbD into its processes. The focus is on quality should be built into a product with an understanding of the product and process by which it is developed and manufactured with understanding risks involved in manufacturing the product and how best to manage those risks. This is improvement is over "Quality by Testing" (QbT), traditional approach, by the Industry. See Table 1.

QbD facilitates design of products and processes that enhances the product's Qurity, Efficacy and Safety in the interest of Patients.

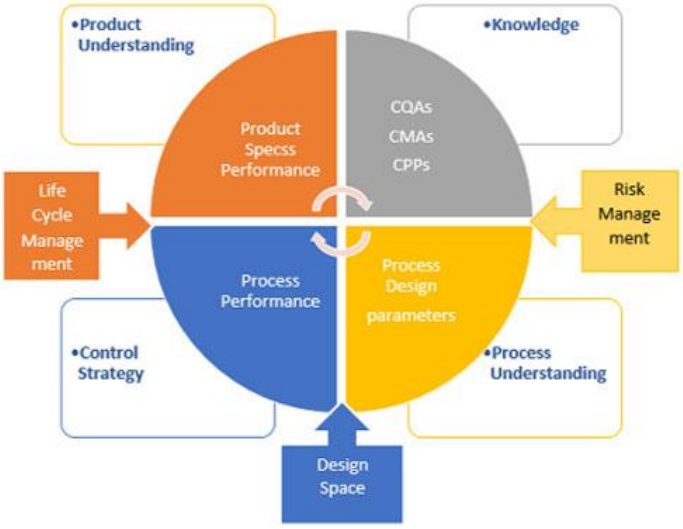


*Diagram 2: Continual Improvement / Life Cycle Management*

While QbD will provide design space (DS), the scale-up and commercial manufacturing experience provides knowledge about the process and the interactions of raw materials used therein with excipients. FDA's Process Validation guidance in January 2011 is for companies to continue benefiting from knowledge gained, and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are addressed.

**International Conference on Harmonization (ICH) Guidelines:**

Working with regulators in the European Union (the European Medicines Agency) and Japan, the US FDA has improved Quality by Design objectives through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH introduced the guidelines:

ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System).

These ICH guidelines improve understanding to build "Quality by Design" into Formulation development. This will ensure that "Quality Risk Management and Knowledge Management" are used to monitor the lifecycle management that maintains process control and product quality. The difference between QbD for New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) products is most apparent at the first step of the process.

**TABLE 1: EXPLAINS ADVANTAGES OF QBD IMPLEMENTATION OVER TRADITIONAL WAYS OF DEVELOPMENT**

| | Traditional | QbD |
|---|---|---|
| Pharma Development | Empirical / Trial & error experiments. | Systematic approach , Design Space, Multivariate experiments. Proactive to Design Quality into the product. |
| Mfg. Process | Fixed process. | Flexible Process within Design Space. |
| Process Controls | In-process controls / Offline Quality testing. | PAT monitored On-line for feedback. |
| Product Specifications | Primary for Quality Control based batch data | Part of overall Control Strategy based on desired product performance / Predictability. |
| Control Strategy | In process checks / quality by testing. | Risk based monitoring. PAT Real Time Release Testing. |
| Life Cycle Management | More on Reactive actions / Post approval changes needed. | Continual Improvement within Design Space based on Feedback feedforward process. |

US FDA defines QbD as "Systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".

QbD is a systematic process to generate Robust processes with the help of Quality Risk Management (ICH Q9). It is important to control the "Variability" of Raw materials as well as in Manufacturing process by identifying Critical Quality Attributes (CQA) / Critical Material Attributes (CMA) and Critical Process Attributes (CPP) through Risk Management process. It helps to have better understanding of Process & Product thus helping Life Cycle Management of the product (LCM) as explained in diagram no.1

## Elements of Qbd

1. Quality Target Product Profile (QTPP) that identifies CQAs of the drug product.

2. Product design and understanding including the identification of Critical Material Attributes (CMAs).
3. Process design and understanding including the identification of Critical Process Parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs.
4. A control strategy that includes specifications for
the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process.
5. Process capability and continual improvement.

**Regulatory agencies objectives for QbD initiatives are to:**

"Encourage early adoption of new technological advances by the pharmaceutical industry. Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance. Encourage implementation of risk-based approaches that focus both industry and the agency attention on critical areas. Ensure regulatory review and inspection policies are based on state-of-the-art pharmaceutical science. Enhance consistency and coordination of the FDA's drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the agency's business processes and regulatory policies concerning review and inspection activities".


*Diagram 3: QbD Implementation steps:*

By obtaining increased process & product understanding in order to identify and monitor critical sources of variability helps to achieve Right First Time Performance. Therefore it is essential we

shift from Compliance to improved Process & product understanding , which will allow QbD of effective and efficient manufacturing process as well as Real Time Quality Assurance.

One of the important goals of QbD is to ensure that all Sources of Variability affecting a process are identified, explained and managed by appropriate measures.(Diagram 1) This enables the finished medicine to consistently meet its predefined characteristics from the start to achieve ”Right first time”. QbD focuses on the use of multivariate analysis, often in combination with modern process-analytical chemistry (PAT) methods and knowledge-management tools to enhance the identification and understanding of critical attributes of materials and critical parameters of the manufacturing process. This enhanced understanding of product and process is used to build quality into manufacturing and provide the basis for continuous improvement of products and processes. Knowledge gained through such process and product understanding helps to monitor Life Cycle Management of the product. Diagram 2 explains process & product understanding to support Continual Improvement.

**Advantages of QbD to the Generic Industry**

- Better understanding of the process and the product.
- Minimum batch failures.
- Better understanding of risks involved & mitigation.
- Minimising variations to achieve consistency in manufacturing quality.
- An enhance QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches for example: Manufacturing changes within the approved design space can be without regulatory review or approval.
- Reduction of post-approval submissions.
- Greater regulator confidence of robust products.
- Innovative Process Validation approaches.
- More drug availability and less recalls from market.
- Improved yields, lower cost, less investigations, reduced testing, etc.
- Timely launch of products.
- Right first time & every time concept.

- Continuous improvement over the total product life cycle.
- Real time Release thru PAT implementation.
- Return on investment / cost savings.
- More efficient technology transfers.

QbD Applications Scope: It can be applied to Drug substance development (ICH Q11); Drug Product (ICH Q8 R2) , Analytical method development. FDA strongly recommends to include QbD elements in ANDA submissions since January 2013. It can be implemented for Biopharmaceuticals products too.

**Quality Culture is the foundation to implement QbD successfully**

- Commitment to quality: Including establishing effective pharmaceutical quality systems & maintaining, modernizing as needed, equipment and facilities.
- Adopt a "Quality Culture": Stress importance of product quality from the top down. Decision making with end-user / patient in mind
- Proactively monitoring products and processes: Using risk- based approaches and modern analytical methods
- Anticipate supply problems: Arrange for additional manufacturing capacity. Develop alternate supplies of components.
- Invest in quality and continual improvement: Quality can pay for itself!

**US FDA has already published two QbD implementation case studies**

1. Quality by Design for ANDAs: An Example for Immediate-Release Tablets April 2012.
2. Quality by Design for ANDAs: An Example for Modified Release Tablets December 2011.

FDA case study is very good example how to implement QbD process for product development along with expected Risk assessments for initial & amended risks monitoring and documentation.

Regulatory Agencies like EMA also initiated the QbD concepts implementation. EU has also released a document for "Real Time Release". The European Medicines Agency (EMA) welcomes applications that include quality by design. Quality by design is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management

methodology in the design, development and manufacturing of medicines. US FDA / EMA refers to ICH guidelines Q8, Q9, Q10, Q11 & Q12 for QbD implementation (3). Now ICH is working on "Q13- Continuous Manufacturing" & "Q14- Analytical Method Development". These new ICH guidelines are expected in near future.

**Industry response to QbD compliance**

"QbD is becoming the norm. The value of QbD principles is clear and will continue to be integrated into the product development processes. QbD is already expanding its scope into new paradigms such as RTRT, continuous quality verification, analytical QbD etc. Industry expects this trend to continue. QbD will continue to grow and become more embedded as it is applied more in production Industry will get better at it. Industry will use more prior knowledge and more risk-based approaches".

**Summary:**

The characteristics of a successful QbD program is:

- Transition from Reactive to Proactive approach to achieve "Right First Time".
- Risk based, Science based approach.
- Primary focus is patient safety and product quality & eficacy.
- Improvement in product & process understanding.
- Improvement in process capability / robustness / consistency in commercial manufacturing.
- Systematic development reducing Re-working & Rejections of the batches.
- Significant reduction in regulatory oversight post approval due to transparent operations.
- Driver to Business Benefits.

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