Enhanced Quality Systems - Quality-by-Design (QbD) approach for Pharmaceuticals

By Dr. Shruti Bhat, PhD, MBA, Enterprise Strategist and QbD Specialist.
Translates concepts to profits, consistently!

Website: www.DrShrutiBhat.com
Email: Shruti.Bhat@Innoworks.ca
Voice: 1.403.969.6219

Definitions and scope of quality systems in pharmaceuticals has evolved over a period of time. The "Thalidomide babies tragedy" prompted the concept of continuous or cGMP. With cGMP came into existence the concept of Quality Assurance or "Zero defect". QA advocated that quality cannot be created at the end of processing, but has to be in-built into a product at every step of manufacturing process.

Further improvements in quality systems throughout the 1990's and beyond brought about concepts of internal audits, documentation and validations. Y2K improved quality systems further...introduced 21CFR part 11 compliance measures. Year 2010 and beyond promises further refinement in quality systems- Quality-by-Design (QbD).

What is quality by design?

Quality by design means designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process.

Where to implement quality by design?

Quality by design implementation targets the following departments within a pharmaceutical company- Management, Procurement, R&D, Manufacturing, Testing, Quality control, Quality assurance, Regulatory, Logistics, Sales, Warehouse/ Supply chain including vendors facilities, CRO and CMO.

Principles of quality by design?

QbD scope assume that problems can be anticipated and their occurrence prevented by reviewing data and analyzing risks associated with operational and quality system processes and by keeping abreast of changes in scientific developments and regulatory requirements. The central goal of a quality system is the consistent production of safe and effective products and ensuring that these activities are sustainable. A robust quality system will promote process consistency by integrating effective knowledge-building mechanisms into daily operational decisions. When fully developed and effectively managed, a QbD system will lead to consistent, predictable processes that ensure that pharmaceuticals are safe, effective, and available for the consumer.

Framework of quality by design?

Quality by design integrates *quality systems* and *risk management* approaches into its existing programs with the goal of providing the necessary framework for implementing *quality by design* (building in quality from the development phase and throughout a product's life cycle), continual improvement and risk management in the drug manufacturing process and also for post development changes and optimization.

Quality risk management (governed by CAPA- corrective actions preventive actions) is a valuable component of an effective quality systems framework. Quality risk management can, for example, help

guide the setting of specifications and process parameters for drug manufacturing, assess and mitigate the risk of changing a process or specification, and determine the extent of discrepancy investigations and corrective actions.

CAPA focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their recurrence. QbD system models discuss CAPA as three separate concepts, all of which are used in this guidance:

- Remedial corrections of an identified problem.
- Root cause analysis with corrective action to help understand the cause of the deviation and potentially prevent recurrence of a similar problem.
- Preventive action to avert recurrence of a similar potential problem.

Review outcomes typically include:

- Improvements to the quality system and related quality processes.
- Improvements to manufacturing processes and products.
- Realignment of resources.

The results of a management review would typically be recorded. Planned actions should be implemented using effective CAPA and change control procedures.

QbD- Design, Develop, and Document Product and Processes:

In a QbD systems manufacturing environment, the significant characteristics of the product being manufactured should be defined from design to delivery, and control should be exercised over all changes. In addition, quality and manufacturing processes and procedures — and changes to them — must be defined, approved, and controlled. It is important to establish responsibility for designing or changing products. Documenting processes, associated controls, and changes to these processes will help ensure that sources of variability are identified.

An important purpose of implementing a quality systems approach is to enable a manufacturer to more efficiently and effectively validate, perform, and monitor operations and ensure that the controls are scientifically sound and appropriate. The goal of establishing, adhering to, measuring, and documenting specifications and process parameters is to objectively assess whether an operation is meeting its design and product performance objectives. In a robust QbD system, production and process controls should be designed to ensure that the finished products have the identity, strength, quality, and purity they purport or are represented to possess.

The design concept established during product development typically matures into a commercial design after process experimentation and progressive modification.

Risk management can help identify areas of process weakness or higher risk and factors that can influence critical quality attributes that should receive increased scrutiny. The QbD framework recommends that scale-up studies be used to help demonstrate that a fundamentally sound design has been fully realized.

A sufficiently robust manufacturing process should be in place prior to commercial production. With proper design and reliable mechanisms to transfer process knowledge from development to commercial production, a manufacturer should be able to validate the manufacturing process.

Conformance batches provide initial proof that the design of the process produces the intended product quality. Sufficient testing data will provide essential information on performance of the new process, as well as a mechanism for continual improvement. Modern equipment with the potential for continual monitoring and control can further enhance this knowledge base. Although initial commercial batches can provide evidence to support the validity and consistency of the process, the *entire product life cycle* should be addressed by the establishment of continual improvement mechanisms in the quality system.

Thus, in accordance with the QbD approach, process validation is not a one-time event, but an activity that continues throughout a product's life.

As experience is gained in commercial production, opportunities for process improvements may become evident, require review and evaluation of records to determine the need for any change. These records contain data and information from production that provide insight into the product's state of control.

Change control systems should provide a dependable mechanism for prompt implementation of technically sound manufacturing improvements. Written procedures are followed and deviations from them are justified and documented to ensure that the manufacturer can trace the history of the product, as appropriate, concerning personnel, materials, equipment, and chronology and that processes for product release are complete and recorded.

Monitor critical processes that may be responsible for causing variability during production. A QbD approach calls for the manufacturer to develop procedures that monitor, measure and analyze the operations (including analytical methods and/or statistical techniques). Monitoring of the process is important due to the limitations of testing. Knowledge continues to accumulate from development through the entire commercial life of a product. **Significant unanticipated variables should be detected by a well-managed QbD system and adjustments implemented.** Procedures should be revisited as needed to refine operational design based on new knowledge. Process understanding increases with experience and helps identify when change will lead to continual improvement.

When implementing data collection procedures, following points have to be considered:

- Are data collection methods documented?
- When in the product life cycle will the data be collected?
- How and to whom will measurement and monitoring activities be assigned?
- When should analysis and evaluation (e.g.trending) of laboratory data be performed?
- What records should be collected?

Under a QbD system, trends should be continually identified and evaluated. One way of accomplishing this is the use of statistical process control.

The information from trend analyses can be used to continually monitor quality, identify potential variances before they become problems, bolster data already collected for the annual review, and facilitate improvement throughout the product life cycle. Process capability assessment can serve as a basis for determining the need for changes that can result in process improvements and efficiency.

A key component in QbD system is handling nonconformities and/or deviations. The investigation, conclusion, and follow-up must be documented. To ensure that a product conforms to requirements and expectations, it is important to measure the process and the product attributes (e.g., specified control parameters, strength) as planned. Discrepancies may be detected during any stage of the process or during quality control activities. Not all discrepancies will result in product defects; however, it is important to document and handle discrepancies appropriately. A discrepancy investigation process is critical when a discrepancy is found that affects product quality.

It is important to develop and document procedures that define who is responsible for halting and resuming operations, recording non-conformities, investigating discrepancies and taking remedial action. The corrected product or process should also be re-examined for conformance and assessed for the significance of the non-conformity. If the non-conformity is significant, based on consequences to process control, process efficiency, product quality, safety, efficacy, and product availability, it is important to evaluate how to prevent recurrence.

QbD systems call for continually monitoring trends and improving systems. This can be achieved by monitoring data and information, identifying and resolving problems, anticipating and preventing problems.

QbD systems procedures involve collecting data from monitoring, measurement, complaint handling, or other activities, and tracking this data over time, as appropriate. Analysis of data can provide indications that controls are losing effectiveness. The information generated will be essential to achieving problem resolution or problem prevention.

cGMP regulations require product review on at least an annual basis Vs a QbD systems approach calls for trending on a more frequent basis as determined by RISK.

Trending enables the detection of potential problems as early as possible to plan corrective and preventive actions. Another important concept of QbD systems is the use of trending to examine processes as a whole.

Elements of RISK should be considered relative to intended use of a product, patient safety and ensuring availability of medically necessary drug products.

Implementation of QbD includes assessing the risks, selecting and implementing risk management controls commensurate with the level of risk and evaluating the results of the risk management efforts.

Since risk management is an iterative process, it should be repeated if new information is developed that changes the need for, or nature of, risk management.

In a manufacturing environment, QbD risk management is used as a tool in the development of product specifications and critical process parameters. Used in conjunction with process understanding, quality risk management helps manage and control change.

Corrective action is a reactive tool for system improvement to ensure that significant problems do not recur. Being proactive is an essential tool in QbD.

Preventive actions will help ensure that potential problems and root causes are identified, possible consequences assessed and appropriate actions considered.

The selected preventive action should be evaluated and recorded and the system should be monitored for the effectiveness of the action...

This white paper is only an introduction of concept of Risk based approach to quality i.e. Quality by design or QbD.

Details of QbD implementation across various departments within a pharmaceutical company is being discussed through different chapters of this white paper.

Coming...

QbD in R&D has changed the entire approach by which pharmaceutical products are developed.

QbD in api development?
in formulation development?
in clinical research?
in analytical research?

While, providing an essential compliance tool, QbD brings about shortening product development time lines and huge savings in research costs!

About the author:

SHRUTI U. BHAT, PH.D, MBA

MANAGEMENT CONSULTANT

Shruti Accelerates ROI …

For the past 18 years, Shruti has been consistently endorsed as - “Thought Leader par excellence”, and “Strategy Expert” spearheading profitable business process improvement initiatives for her clients.

Her mantra is to "Create a Positive Change" in an organization by providing "Strategic, Substantial and Pragmatic advise" to meet organization’s "Fast to Market", "Lean Processes" and “Super-Profit” objectives.

Shruti has her handle on Enterprise wide strategy including- Business strategy, Business process re-engineering & continuous improvement, Intellectual property management & capitalization, Organizational leadership & team development, Market expansions, mergers & acquisitions, Startup & early stage business development & growth, Quality risk management, Quality by design, Strategic alliances & Business process outsourcing. Through her customized “ROI strategy design”, Shruti provides cutting-edge concepts of innovation to create affordable quality products that are "Tough to copy".

She is a gold-medalist, with PhD, MBA from ITM- Southern New Hampshire University School of Business, USA with numerous patents and publications to her credit.

She is an invited keynote speaker at several international conferences and workshops. She blogs ardently and contributes her thoughts to journals, magazines & newspapers.

Reach Shruti at-
Website: www.DrShrutiBhat.com
Email: Shruti.Bhat@Innoworks.ca
Voice: 1.403.969.6219