Review Article

Brief Note on the 5WS and 1 H Of QBD Implementation

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ABSTRACT

Quality by Design (QbD) is all about doing things determinedly with better understanding of the process and product. In Pharmaceutical development this is a risk assessment through systematic approach with well-defined product quality. QbD gives scope for continued improvement of the product / process throughout the life cycle of product and minimize the risk of variation filling so in worst case scenario product recall from the market. This novel approach builds the quality into the product not by testing but through planning. QbD starts with setting a Quality Target Product Profile (QTPP) and identifying the Critical Quality Attributes (CQA). Then risk assessment is done for both critical material attributes and the process attributes to identify the factors affecting the quality of the final product and a link is established with the CQA to prepare the design space with the help of design of experiment. The source of variability need to be controlled by application of control strategy and the quality by design implementation enables flexibility in manufacturing process. Moreover iimplementation of QbD has been proved to be beneficial both for regulatory bodies and pharmaceutical industries is the providing medication sifts for purpose to the patients. This holistic systematic approach will change the research strategies including clinical research.

Keywords: Quality by Design (QbD), Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), Design Space, Control Strategy, Design of experiment (DoE).

INTRODUCTION

What is QbD?

Pharmaceutical field is strictly regulated by various regulatory authorities or agencies like FDA, MHRA and EMA etc., to monitor the quality of the products before entry to the market. Even if pharmaceuticals have greatly improved on quality there is still some element of risk to the patients, hencethere is a need for continuous quality improvement.

Quality as per ICH Q8 is the appropriateness of a drug substance or product for its anticipated use. This term comprises such aspect as the uniqueness, strength and pureness.

According to Janet Woodcock quality is free of impurity and reproducible delivering the therapeutic benefit assured in the label to the end user.

Pharmaceutical Quality is a function of drug substance, excipients, manufacturing, and packaging.

Quality as per QbD can be built into the product not by testing but through design.

So QbD is defined by as a methodical approach to development which begins with defined process and accentuate product, process cognizance and process control, based on quality risk management and sound science.

As per Janet Woodcock Quality by Design "Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches." (Yu, 2013)

Who has Outlined QbD?

History

Quality by Design (QbD) is a notion first outlined by renowned quality expert Joseph M. Juran in various journals, most especially Juran on Quality by Design. Juran said quality could be pre-planned, and that major quality disasters and problems link to the way in which quality was planned in the beginning. The concept of QbD was stated in the ICH Q8 guidance, which cites "quality cannot be tested into products", i.e., "quality should be built in by design" (P, Nishendu; V Rakshit; N Vidhi kalola; Patel Parula B, 2012).

Concept to Achieve Quality prior to QbD

Product quality is critically monitored even before the quality by design concept, which is known as "Quality by Testing". In quality by testing quality is guaranteed by a fixed manufacturing process, raw material testing, in-process material testing, and end product testing. The quality of raw materials counting drug substance and fillers is supervised by testing. If they meet the manufacturer's anticipated and FDA defined specifications or further standards such as USP for drug constituent or fillers, they can be used for the manufacturing of the products.

Due to uncertainty, whether the drug substance specification alone is adequate to assure quality, the drug constituent manufacturing process is also securely controlled. A change to the drug constituent

manufacturing process may necessitate the drug manufacturer to file supplements with FDA. Finished drug products are verified for quality, if they meet specifications of manufacturer and FDA. If not, they are rejected. Root source for failure are generally not well understood or analysed. The risk of loss due to deviation from specification is high due to non-availability of proper investigation for the cause of deviation. The critical parameters for final product testing are assay, content uniformity, impurities, moisture, and dissolution. Thus there is hardly any scope for continuous improvement in the product quality in this quality by testing method. (C. Hubert, P. Lebrun, S. Houari, E. Ziemons, E. Rozet, Ph hubret, 2014) (USFDA, CFR - Code of Federal Regulations Title 21, 211.165, 2015).

When Regulatory Agency Adopted QbD?

In 2002, FDA declared new initiatives "Pharmaceutical GMP initiatives for 21st century a risk based approach. The purpose of this initiative was to promote the adoption of advanced technology, facilitate the application of quality management techniques, encourage risk based approach and ensure quality guidelines. Recently these guidelines have been named "Pharmaceutical quality for 21st century a risked based approach. (USFDA, Pharmaceutical CGMPS for the 21st Century A Risk-Based Approach, 2004) ICH Q10 the pharmaceutical quality system defines one broad model for an effective pharmaceutical quality system which is based on International Standards Organization (ISO) quality concepts. It also includes Good Manufacturing Practice (GMP) regulations which complements Pharmaceutical Development (ICH Q8) and Quality Risk Management (ICH Q9). ICH Q10 is a model for pharmaceutical quality system that can be executed throughout the different junctures of a product lifecycle which aid innovation and continuous improvement and strengthen the association between manufacturing activities and pharmaceutical development. (ICH, Pharmaceutical Development Q8(R2), 2009) (ICH, ICH guideline Q9 on quality risk management, 2015).

Whom to Approach - QbR (Question-based Review)?

For quality and safety purpose The Food and Drug Administration (FDA) has established a Question based Review program (QbR) intended for chemistry, manufacturing, and controls (CMC) evaluation of abbreviated new drug applications (ANDAs). The QbR is a physical implementation of the concepts in the GMP for the 21st Century initiative that boosts current CMC assessment of pharmaceutical quality in three respects:

1. By directing assessors to ask the right questions, it enhances their critical review with a specific emphasis on quality by design, and enables them to identify only those deficits in CMC information which affect product quality.
2. By inspiring sponsors to share their pharmaceutical development knowhow, it encourage holistic approach for understanding of how formulation and manufacturing process influence pharmaceutical quality, which leads to more pertinent specifications and manufacturing controls.
3. By having a risk assessment section, which will link regulatory scrutiny to the level of rational understanding and dosage form intricacy, supporting continuous improvement and innovation. It is expected to eliminate up to 80% of CMC supplements, and free up scarce resources.

Thus the proposed QbR will result in assessments that focus on important features of drug product quality and inspire reviewers to identify about specifications and manufacturing controls are required to ensure product quality.

It also results into risk assessment for that product.

Futuristically, the CMC review will provide additional information about specifications connected to product quality, risks associated with the manufacturing and formulation of product and why FDA is assured that the product can be manufactured homogeneously. (Iser, 2015)

Where to Implement QbD?

Figure 1: QbD Fingerprint

Figure 1 represents the QbD fingerprint of various Stake holders. Some of the important stakeholders of Quality by design implementation within a pharmaceutical company are Management, R&D, Testing, Regulatory, Manufacturing, Logistics, Procurement, Quality control, Quality assurance, Sales, Warehouse/Supply chain including vendor's facilities, CMO and CRO (Bhat, 2010).

R & D

1. Defines basis for formulation, process and product design.
2. Capture relationship between critical process parameters (CPP) and critical to quality product attributes (CQA).

Scale-Up & Technology Transfer

1. Generate detailed characterization of process and product being transferred even upon scale up.
2. Establish the capability to manufacture product homogeneously and predictably to the required quality and cost, in agreement with appropriate regulations. Ensures relationship between CPP and CQA.

Manufacturing

The research and development stage is defined by accomplishment of a development plan consisting of a number of distinct experiments that are designed to formulate, establish defined manufacturing process and provide process and formulation understanding around the key association between parameters and attributes.

When the product is considered for manufacturing, it will most likely face a much wider range of disparity on the parameters than seen in development.

For example, attribute variability may increase due to a wider kind in incoming raw material parameters that can't possibly be captured in R&D. It is upon transfer to Manufacturing that review of the actual process capability and robustness as well as any process enhancement or remediation will begin.

Manufacturing results a large amount of practical process performance data that may be used for a variety of purposes.

It should be periodically reviewed to assess process capability, robustness and to prioritize improvement efforts; the data should be reviewed to identify relationships.

Feedback to R&D to be made simultaneously during these activities to ensure building quality into the design process.

Post-Manufacturing

After an adequate time of manufacture, the commercial scale review of sturdiness can be ascertained.

Realize process capability and modify process if necessary to improve robustness.

Confirm relationship between CPP and CQA.

How is QbD Implemented?

Various steps of implementing QbD is summarized in below Figure 2.

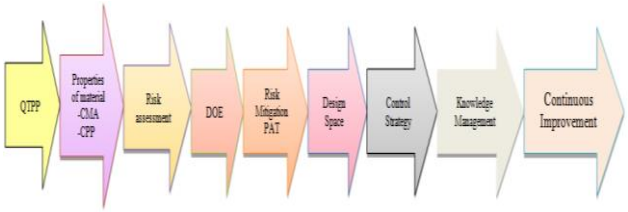

Figure 2: Steps of Implementing QbD

Step 1

Quality Target Product Profile & Product designed to meet patient needs

Quality Target Product Profile (QTPP) is generally acknowledged as a tool for setting the strategic basis for drug development "planning with the end in mind which is fit for purpose." Lately a long drawn out use of the QTPP in development plan, clinical and commercial resolution, regulatory agency exchanges, and risk management has started evolving. The target profile is a summarised drug development program termed in the context of suggested information goals Quality Target Product Profile (QTPP) is a term that is an accepted extension of TPP in terms of product quality. It is the quality physiognomies that the drug product should retain in order to reproducibly deliver the healing benefit assured in the label. (Moheb M. Nasr, 2011) (Anurag S Rathore, 2009)

Definition of QTPP ? (Jennifer Maguire, 2015)

Quality Target Product Profile is the first step towards the product development. Normally QTPP can be defined:

- Before start of development
- After RLD and API characterization
- As per market or client requirement
- Before Formulation and Process Development

Quality Target Product Profile (QTPP) Includes

The quality target product profile forms the base of design for the product development. QTPP could include:

- Anticipated use in clinical setting, route of administration, dosage form, delivery methods;
- Strength(s) of Dosage;
- Method for Container closure;
- healing component release or delivery and attributes influencing characteristics e.g., dissolution, aerodynamic performance suitable for the drug product dosage form being developed;

Criteria for drug product quality (e.g., sterility, purity, stability and drug release) appropriateness for the promoted product.

Step 2

Understand physical, chemical, microbiological and biological properties of materials

As per ICH Q8 Critical Quality Attributes is a physical, chemical, biological, or microbiological characteristic that should be within relevant limit, range, or distribution ensuring the intended product quality.

CQAs are largely associated with the drug substance, intermediates/fillers (in-process materials) and drug artefact. Physical properties of materials include physical

description, appearance, and flow property. For a drug substance, particle size, its salt form, polymorphism, aqueous solubility and melting point are very important parameters which affect quality of final dosage form. Chemical properties includes pKa of drug substance, stability in solid states (crystalline & amorphous), and in solution state. Biological properties which are important in quality determination of drug product comprise partition coefficient, membrane permeability, and Bio pharmaceutics Classification System. (Stangler, 2011)

Critical Material Attributes

A physical, chemical, biological (and/or microbiological) property or characteristic of raw material that should be within relevant limit, range or distribution to assure the intended quality of drug substance and in process materials.

Critical Process Parameter

Process parameter(s) consistency has an impact on a CQA and therefore should be monitored and controlled to ensure that the process produces the absolute quality. So parameter is critical when a sensible change in that parameter causing the product to fail to meet the QTPP. Therefore a parameter is critical or not depends on how huge a change one is willing to consider.

Step 3

Risk Assessments

Quality risk management is a methodical process for the evaluation, control, communication and analysis of risks to the quality of the medicinal drug product throughout the product lifecycle. Risk assessment comprises of the identification of potential hazards and the analysis or evaluation of risks associated with exposure to identified potential hazards. Quality risk assessments commence with a well-framed problem description or risk. Risk assessment is normally performed early in the pharmaceutical development process.

Risk assessment tools can be applied in identifying and ranking parameters (e.g., process, equipment, input materials) with potential to have an influence on product quality, based on past knowledge and initial experimental data or facts. Once the significant parameters are identified, they can be further planned to achieve a higher level of process understanding. This process of linking material attribute and process parameter to critical quality attributes done mainly through design of experiment can also be described as working within the design space. (Lawrence X. Yu, corresponding author Gregory Amidon, Mansoor A. Khan, Stephen W. Hoag, James Polli, G. K. Raju, and Janet Woodcock, 2014).

Objective of Risk Assessment

- Agreement on process scope.
- Adopt what's important to evaluate.
- Prioritize risk based parameters.
- Agreement on high level experimental approach.
- Identifying and prioritizing PAT applications.

Risk assessment is a helpful scientific process applied in quality risk management that can assist in identifying which material and/or process parameters have an effect on product CQAs.

Step 4

DOE (Design of Experiment)

Design of experiments (DOE) technique empower designer to define simultaneously the specific and interactive influence of many factors that could influence the output result in any experiment. DOE also provides a full understanding of interaction between design elements.

Therefore, it helps turn any standard design into a robust one. Also DOE helps to pin point sensitive parts and sensitive areas in design that cause problem in yield. Enable Designs to fix the problems and produce robust design and higher yield before production. DOE begins with the end in mind with a holistic overview and a systematic approach. It defines the responses (QTPP/CQAs), List all probable process parameters and material attributes that may impact the responses being analyzed and based on process knowledge risk parameters are identified.

DOE is a statistics-based multivariate approach. It has good coverage of space and methodology to achieve a predictive knowledge of a complex process with the fewest trials possible.

It is a principal tool to determine the relationship between the factors that have an effect and the response of that process. Study reveals that the DOE helps increase yield of pharmacological intermediate from 70% to 88%. (Codexis Laboratories, 2012)

Step 5

Risk Mitigation

This process comprises of corrective actions considered to resolve the incident and preventive actions proposed to avoid a repetition of the incident in the future.

Again risk control will also include consideration of risk acceptance for the measures put in place and will eventually need to be accepted or rejected. PAT tools may be used to mitigate risk.

Many tools are available that enable process understanding for methodic, risk managed pharmaceutical development, manufacturing, and quality assurance.

These tools, when implemented within a system, can provide effectiveness and efficient means for recording information to help process understanding, continuous improvement, and development of risk-mitigation approaches.

In the PAT framework, these tools can be classified according to the following:

- ✓ Multivariate tools for design,
- ✓ data acquisition and analysis,
- ✓ Process analyzers,
- ✓ Process control tools,
- ✓ Continuous improvement and knowledge management tools

Correct combination of some, or all, of these tools may be applied to a single-unit operation, or to an entire manufacturing process and its quality assurance.

Process analytical Technology (PAT)

The term "Process Analytical Technologies (PAT)" has been used to describe "a system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality".

The PAT focuses on developing quality into the product and manufacturing processes, as well as continuous process improvement. (U.S. Department of Health and Human Services, 2004)

Step 6

Develop Design Space

The link between the process inputs (material attributes and process parameters) and the critical quality attributes can be defined in the design space which is very useful in the development process. The risk assessment and process development experiments also lead to definition of the linkage and effect of process parameters and material attributes on product CQAs, and also help identify the variables and their ranges within which reliable quality can be accomplished. Identified process parameters and material attributes can then be selected for inclusion in the design scope. Knowledge gained from studies should be labelled in the submission.

It is helpful to govern the edge of failure for process parameters or material attributes, above which the relevant quality attributes, cannot be achieved.

However, determining the edge of failure or demonstrating failure modes are not necessarily parts of establishing a design scope. Design scope helps in developing a flexible formula with lesser risk of product failure.

The design space can be established through the experimental design in DOE. (Chatterjee, 2012)

Step 7

Establish Control Strategy

The control strategy is "a defined set of controls, derived from current product and process understanding that ensures process performance and quality.

The controls can have parameters and attributes linked to drug substance and drug product materials, components, facility, equipment, operating conditions, in-process controls, finished product specifications, and the associated methods and occurrence of monitoring and control.

A control strategy is designed ensuring a product of required quality can be produced consistently.

A comprehensive pharmaceutical development approach will yield process and product understanding and identify cause of variability.

Origin of variability that can influence quality should be identified, appropriately understood, and later controlled.

Understanding origin of variability and their influence on processes or processing, in-process materials and drug product quality can give an opportunity to swing controls upstream and minimizing the need for end product testing.

The combination of product and process understanding, quality risk management (ICH Q9), will support the control of the process in a manner that the variability can be compensated for in a compliant manner to deliver consistent product quality.

(Robert A. Lionberger, Sau Lawrence Lee, LaiMing Lee, Andre Raw, and Lawrence X. Yucorresponding author, 2008)

A control strategy may include the followings:

- Controlling input material attributes, e.g., drug substance, excipients, and primary packaging materials based on an understanding of their influence to product quality.
- Specifying the Product
- Controlling unit operations that have impact on downstream processing or product quality (e.g., the influence of drying on degradation, particle size dissemination of granulate on dissolution etc.)

Step 8

Knowledge Management:

Knowledge management, as defined in ICH Q10, is a "systematic approach to acquiring, storing, and disseminating information related to products, manufacturing processes, and components."

In other words, it is the life-blood of QbD. Without knowledge management, QbD becomes an event instead of an on-going process.

Every day that a product is being manufactured, there is something to learn about the process and the product.

Capturing and sharing that information with operations, quality, and research and development are the value of

knowledge management. The learning should attribute to quality enhancement in production and further bring about improvement in the development of future products. (Lipa, 2011)

Step 9

Continuous Improvement

Continuous improvement is a vital element in a modern quality system that targets at improving efficiency by optimizing process and eliminating futile efforts in production.

These efforts are principally aimed at reducing variability in process and product quality characteristics. QbD emphasises on building quality into the product as well as manufacturing processes continuous process improvement and reduction of variability.

The pillar for Continuous Improvement is the Pharmaceutical Quality System. PQS should provide continuous improvement and help to recognise and implement suitable product quality perfections, process improvements, variability reduction, inventions and pharmaceutical quality system improvements, thereby increasing the capability to fulfill quality needs steadily.

Quality risk management can be useful for recognizing and prioritizing areas for continuous improvement. "Continuous improvement is not the same as Corrective Actions Preventative Actions (CAPA).

CAPA's follow when product quality physiognomies are in question (e.g., out of specification).

For constant improvement efforts, products should already be in agreement with their specifications and process improvement phases should be within the original "design space".

Examples of Continuous Improvement comprise fine-tuning a set point of a process, advanced control methods, different equipment of the same design, re-designing a process stage, altering a working process, LEAN initiatives, streamlining documents, bringing automation in the process, connecting on-line measurements, eliminating unit operation, altering the design space and apprising the Control Strategy. (Jain, 2014)

Why QbD is Important?

Potential benefits of QbD: (Potential benefits of QbD, 2012)

- **The cost to implement QbD is minimal:** QbD allows enhanced planning, cycle time, yield and quality. Some claimed the QbD has reduced technical development costs by up to 25% per program.
- **Improved quality and lower risk:** Employing QbD is indeed using good science, that leads to over all improvement and more reliable product.
- **Increased sales:** Products that employ QbD have superior launches and will have enhanced product design leading to rarer stock-outs.
- **QbD will not escalate the timeline for development:** QbD may add an insignificant amount of time during the initial development phase, yet there is no consequence on time consumed in critical path, and time in technology transfer and scale up were mostly reduced. Although QbD may cause minimal increase in time upfront, many companies acknowledged time savings downstream especially for regulatory approvals.
- **Continual Improvement of quality:** It gives scope for the flexibility in manufacturing procedure and continual improvement of the product quality which is beneficial for the patient.
- **Scale up:** To improve quality of products due to fewer batch failures, fewer recalls for stability issues, fewer scale-up failures and minimize product withdrawals from market.
- **Ease of site transfer :** Processes developed using QbD principles are easier to transfer between sites

Comparison of Traditional and QbD Approach (Winkle, 2007) (ICH Q, 2009)

Table 1: Comparison; Traditional Vs QbD approach in Pharmaceutical Development

Aspects	Traditional	QbD
Pharmaceutical Development	**Empirical**; Mostly univariate experiments	**Systematic**; multivariate experiments
Manufacturing Process	**Fixed**	**Adaptable** within design space/specs; prospects for innovation **(PAT)**
Process Control	In-process testing go/no-go; offline investigation with slow response	**PAT employed** for feedback and feed forward on real time
Product Specification	Prime means of quality control; established on batch data	Part of the overall quality control approach; based on anticipated product performance (safety and effectiveness)
Control Strategy	Mainly by transitional and end product testing	**Risk-based**; controls shifted upstream; concurrent release
Lifecycle Management	**Reactive to problems**; post-approval changes required	**Continual improvement** empowered within design space

CONCLUSION

Quality by design is a crucial part of the contemporary approach to pharmaceutical quality.

The Office of Generic Drugs (OGD) has made vital moves to incorporate QbD concepts into ANDA drug filing procedure by implementing a Question Based Review (QBR) structure. Process analytical technology, design of experiment and risk assessment is the tools of QbD concept. Pharmaceutical regulatory bodies are encouraging the industry to implement the Quality by Design approach globally.

This novel approach will be beneficial for the pharmaceutical industries, regulators and patients.

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