ABSTRACT

Quality by design is an essential part of the modern approach to pharmaceutical quality. Quality by Design (QbD) is everything you do to directly to promote, prove safety, efficacy and quality of your product from proof of concept to the point at which customer are buying on regular basics. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product’s life cycle. QbD has become the answer to assist both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development. The concept promotes industry’s understanding of the product and manufacturing process starting with product development, basically building quality in and testing it. As results of all understanding, a company can continually monitor and update its manufacturing process to assure consistent product quality. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality. This systematic approach to product development and manufacturing has received a great deal from traditional approach, which was extremely empirical. Implementation of QbD is enabling transformation of the chemistry, manufacturing, and controls (CMC) review of Abbreviated New Drug Applications (ANDAs) into a modern, science and risk based pharmaceutical quality assessment.

Key words: - quality by design, ICH Q8, ICH Q9, ICH Q10.

INTRODUCTION

Quality “Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes.” [18]
“Quality by Design” A 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. Quality by Design is everything you do to improve safety, efficacy and quality of your product from proof of concept to the point at which customers are buying it on a regular basis. ICH Q8 (R2)

**Aspiration of quality by design**
- To develop a process that can accommodate the range of acceptable variability for maintaining product quality.
- The goal of QbD is to develop robust, well-understood processes that deliver a product meeting the QTPP and are controlled by defined steps within the manufacturing process and that allow for manufacturing process changes within an established design space of input variables and operating parameters without negatively affecting process attributes or identified CQAs.

**Regulatory aspects and need of QbD**
Aspire of implementation of QbD is maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight’. Working on the Quality Topics within International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), created a vision for the future pharmaceutical quality system and the ICH Q8, Q9 and Q10 guidance documents. The ICH vision recognizes that industry and regulatory agencies will benefit from QbD by enabling them to priorities and allocate resources more efficiently, while patients will benefit from improved access to medicines and an enhanced assurance of quality. Although considerable progress has been made in developing a guidance framework that offers the pharmaceutical industry opportunities to adopt modern manufacturing practices, the pace of change in the industry appears slower than might be expected. There may be a number of reasons for this, for example: A company is committed to implementing QbD; but development times for new products mean that it may take several years from the application of QbD principles until a marketing authorization application is submitted for approval by a regulatory agency. A company is open to QbD, but is unsure how to proceed. It adopts a wait-and-see strategy because the QbD principles described in the guidance documents are optional, and it wants to determine how and where
to implement QbD, when regulatory agency expectations are clearer. A company continues with the current quality paradigm because the QbD principles described in the guidance documents are not mandatory. It judges that the role for QbD is inadequate for its products or business, or perhaps it doubts that the reduced regulatory burden and other benefits can be realized in all markets around the globe because of differences in regulations. Implementation of a new paradigm like QbD is likely to represent a significant challenge for many, if not all, pharmaceutical companies.

Table no 1. Benefits to FDA and Industry for implying of QbD

<table>
<thead>
<tr>
<th>Sl. no</th>
<th>FDA</th>
<th>INDUSTRY</th>
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<tbody>
<tr>
<td>1.</td>
<td>Enhancing the scientific foundation for product review</td>
<td>Fewer problems/excursions in manufacturing</td>
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<tr>
<td>2.</td>
<td>Better coordination between review, compliance and inspections</td>
<td>Reduces the number of manufacturing supplements</td>
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<tr>
<td>3.</td>
<td>More consistency and flexibility in regulatory decision making</td>
<td>Relies more on process, and understanding and mitigation of risk</td>
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<td>4.</td>
<td>Decision making based on science</td>
<td>Enables continuous improvements in products and manufacturing</td>
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<td>5.</td>
<td>Improving information in regulatory submissions. Etc.</td>
<td>Relates manufacturing process to the clinic during design. Etc</td>
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ICH consensus vision on Quality/Regulatory guidance documents facilitating QbD

“Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science”

QbD: Regulatory tools

- Q8 Pharmaceutical Development: “The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality”
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System
- Q11 Development and Manufacture of Drug Substances
Table no 2.

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Date</th>
<th>Guideline reference</th>
<th>Scope</th>
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<tbody>
<tr>
<td>1</td>
<td>Nov 2008</td>
<td>ICH Q8 (R1)</td>
<td>Pharmaceutical Development.</td>
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<tr>
<td>2</td>
<td>Aug 2009</td>
<td>ICH Q8(R2)</td>
<td>Pharmaceutical Development</td>
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<td>3</td>
<td>Nov 2005</td>
<td>ICH Q9</td>
<td>Quality Risk Management</td>
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<td>4</td>
<td>June 2008</td>
<td>ICH Q10</td>
<td>Pharmaceutical Quality System</td>
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<td>5</td>
<td>Jan 2011</td>
<td>FDA</td>
<td>Process validation. General principles and practices</td>
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<tr>
<td>6</td>
<td>Dec 2011</td>
<td>ICH Q8/Q9/Q10 (R2)</td>
<td>Guide for implementation</td>
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<tr>
<td>7</td>
<td>March 2012</td>
<td>EMA/CHMP/QWP/</td>
<td>Real Time Release Testing</td>
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<tr>
<td></td>
<td></td>
<td>811210</td>
<td>(formerly GL on parametric release)</td>
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<tr>
<td>8</td>
<td>March 2012</td>
<td>EMA/CHMP/CVMP/QWP/</td>
<td>Process validation</td>
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<td>70278 (draft)</td>
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<tr>
<td>9</td>
<td>May 2012</td>
<td>ICH Q11</td>
<td>Development &amp; Manufacture of Drug Substances</td>
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**QbD Approach – Q 8(R1)**

- Target the quality product profile (QTPP)
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment application of common risk management tools
- Develop a design space = understand the relative impact of input variables (process steps, process parameters, and raw materials) on CQAs.
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

**Elements in QBD**

- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQA)
- Risk Assessment
- Design Space
- Control Strategy
• Lifecycle Management

![Diagram of product or process design and development steps](image)

**Fig no1.**

**Quality Target Product Profile (QTPP)**

A prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product is realized. (ICH Q8 (R2))

The target product quality profile (TPQP) is a quantitative surrogate for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process. It should include quantitative targets for impurities and stability, release profiles (dissolution) and other product specific performance requirement and also includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g., sterility and purity) appropriate for the intended marketed product. The concept of TPP in this form and its application is novel in the QbD paradigm. TPQP is a term that is a natural extension of TPP for product quality. It is
the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The TPQP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label

Table no 3.

<table>
<thead>
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<th>Define - Target Product Profile</th>
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<tr>
<td>• Efficacy</td>
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<td>• Safety</td>
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<td>• Manufacturability</td>
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<tr>
<th>Establish - Critical Quality Attributes</th>
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<tr>
<td>• Science based and prior experience</td>
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<tr>
<td>• Linked to TTP</td>
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<td>• Susceptible to variability</td>
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<tr>
<th>Conduct - Risk Assessment</th>
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<tbody>
<tr>
<td>• Link RM attributes and CPP to CAQ’s</td>
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<tr>
<td>• Impact on safety and efficacy</td>
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<td>• Rank order by criticability</td>
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<tr>
<th>Verify - Design Space</th>
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<tr>
<td>• Critical process parameters</td>
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<tr>
<td>• Process execution requirements</td>
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<td>• Process performance attributes</td>
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<th>Implement - Control Strategy</th>
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<tr>
<td>• In-process and end process controls</td>
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<td>• Use of inline and off line controls</td>
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<td>• Real time release</td>
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<th>Practice - Continuous Improvement</th>
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<tr>
<td>• Continuous quality verification</td>
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<td>• Change within/outside design space</td>
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<td>• Risk-appropriate regulatory approach</td>
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The QTPP is derived from the desired labeling information for a new product. Pharmaceutical companies will use the desired labeling information to construct a target product profile that describes anticipated indications, contraindications, dosage form, dose, frequency, pharmacokinetics and so on. The target product profile is then used to design the clinical trials, safety and ADME studies, as well as to design the drug product that is the QTPP[3].

**Critical Quality Attribute**

“A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure the product meets its intended safety, efficacy, stability and performance” ICH Q8 (R2)

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP observed or predicted in the potential operating space (POS).

\[
\text{Process capability index (CpK) = Upper limit of specification - Lower limit of specification} \div \frac{6 \text{ standard deviation}}{6}
\]

If the CpK is significantly greater than one, the process is defined capable. If the process capability is low, Rath and Strong [19] recommend an iterative five step procedure to progressively reduce the variability of the process. These five steps are:

I. Define: The intended improvement should be clearly stated
II. Measure: The critical product performance attributes should be measured to see if they are out of specification and used to the sigma level of the process.
III. Analyze: When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability.
IV. Improve: The process should be redesigned and/ or process controls should be incorporated to eliminate or attenuate the significant root causes of variance.
V. Control: The improved manufacturing process should be evaluated and maintained.
ICH Q9 discusses the role of risk management in pharmaceutical development as follows:
To select the optimal product and process design, to enhance knowledge of product performance over a wide range of material attributes. Processing options and process parameters. To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API)-starting materials, API’s, excipients and packaging materials. One role for management in QbD is to ensure that teams utilize risk assessment tools that are capable of providing risk- and science-based reviews at critical in the R&D lifecycle. One such critical is prior to finalization of process technology, synthetic route or a qualitative formulation. Decisions made at these will generally impact the quality and costs attributes to a much greater extent than decisions made during process development and later in the product lifecycle. Process understanding is achieved when the relationship between critical quality attributes (CQAs, y) and all the sources of variation (x) in the manufacturing process are understood:

\[ y = f(x) \]

The principle sources of quality variations or inputs to a process include
• 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 ($\sigma$) of the average batch data is a function of all sources:[4]

$$\Sigma \text{Total} = f (\sigma \text{Material} + \sigma \text{Process} + \sigma \text{Equipment} + \sigma \text{Measurement} + \sigma \text{Environment} + \sigma \text{Person})$$

FMEA (failure modes and effects analysis) or use of a prioritization matrix is helpful in identifying the process inputs that impact on quality attributes. In some cases, a deeper dive into the driving forces at critical control points in the manufacturing process can yield a more fundamental understanding of sources of variation.[14]

Failure mode analysis:

$$\text{RPN (risk priority number)} = \text{probability} \times \text{impact} \times \text{detectably}$$

Once the CQAs and process performance attributes (PPAs) are associated with inputs to the process, through a risk assessment process, experiments can be efficiently designed to develop predictive models and confirm causal relationships.[1]

$$Y_i = f(x_1, x_2, \ldots x_n)$$

Analytical Method and Risk Management[18]

$$\text{Risk Factor} = \text{Severity} \times \text{Occurrence} \times \text{detectability}$$

Severity = Effect on Patient
- Related to safety or efficacy (CQAs)
- Different than impact of a manufacturing failure
  - Likelihood of Occurrence = Chance of Failure
- Related to product and process knowledge and controls
- Includes uncertainty for new processes or process changes
Delectability = Ability to Detect a Failure

- Appropriateness and capability of analytical method
- Sampling considerations

Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality ICH(Q8) [2-3]. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8(R2). Product process that impart product quality, safety/ efficacy are collectively known as Design Space. Changes within Design Space do require regulatory review or approval. After the process design space has been established and validated, the regulatory filing would include the acceptable ranges for all key and critical operating parameters that define the process design space in addition to a more restricted operating space typically described for drug products.

Control strategy

- Risk-based approach
- Quality Control may be shifted upstream
- May allow reduced end product testing
- Allows real-time testing

The ability to evaluate and ensure the quality of in-process and/or final product based on process data which typically include a valid combination of measured material attributes and process controls. ICH Q8(R2).

Control strategy is defined as “a planned set of controls, derived from current product and process understanding that assures process performance and product quality”. The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements: procedural controls, inprocess controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach [14].
**Lifecycle management**
Quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics.”

QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability. The backbone for Continuous Improvement is the Pharmaceutical Quality System (PQS). PQS should facilitate continual improvement and help to: “Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement. “Continuous improvement is not the same as corrective actions preventative actions (CAPA). CAPA occur when product quality characteristics are in question (e.g., out of specification). For continuous improvement efforts, products should already be in compliance with their specifications and process improvement steps should be within the original "design space”

**Implementation of Process Analytical Technology**
This is a qualitative tool to measure quality in a continuous process to check out critical quality attributes points where quality get critical by using Process Analytical Technology. Process Analytical Technology in pharmaceutical production checks the quality of the raw material attributes both physically and chemically, that too off-line, in-line or on-line. PAT is a system for design, analysis, and control of manufacturing processes, based on continuous monitoring/rapid measurements of critical quality and performance attributes of raw material, intermediates and products. PAT involves measurement science by using conventional process sensors such as pressure, temperature and probes. The use of process analytical technology can provide huge benefits to pharmaceutical industry by increasing product quality while delivering superior asset utilization and financial value [23].

**Advantages of QbD**
- Better in innovation due to the ability to improve process
- more efficient tech transfer to manufacturing
- less batch failures
• greater regulatory confidence of robust product
• risk based approach and identification
• innovative process validation approaches
• for the customer greater product consistency
• more product available and decreased failure or rejects
• Improved yields, lower cost, less innovation, reduced testing.
• Cost saving and efficient for industry.

Remarks of QBD
• Real time release testing and non-traditional testing
• techniques provide valuable information for in-process control and improvement
• Regulatory flexibility is achievable by applying QbD approach, but requires High degree of process, product and analytical method understanding
• Robust quality systems
• Applicants are encouraged to discuss ‘novel’ QbD implementation approaches with the agency prior to submission
• Need to continue to ensure collaboration and coordination between inspectors, compliance and review
• Need training, training, training –both internal and external
• Need to determine how best to handle legacy products in line with those products issued under QbD Need a “regulatory agreement” or post market management plan

CONCLUSION
The Quality by design project aims to encourage and support quality and to stimulate further thinking about the best ways, to broaden knowledge about best practices in policy. 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. The authors of ICH Q10 foresaw the need to provide guidance on a modern quality system that would be critical to support QbD and continuous improvement of pharmaceutical products over their lifecycle. The science of product development and manufacturing for pharmaceutical products is not as advanced as in other industries such as chemicals, aircraft, petroleum, and engineered products, where “Quality by Design” concepts are applied more routinely. Application of
QbD principles facilitate development of quality products and their assessment throughout their lifecycle, and ultimately, result in greater patient benefit.

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