A CRITICAL ANALYSIS OF ANALYTICAL DESIGN QUALITY

Deepak Gupta
Research Scholar
Department of Pharmacy
Sunrise University, Rajasthan.
deepakpharmacare@gmail.com

Dr. Tushar Treembak shelke
Research Guide
Department of Pharmacy
Sunrise University, Rajasthan.

ABSTRACT

With predetermined goals as its starting point, the quality-by-design (QbD) method employs science and risk management techniques to build a knowledge of the product and process, leading to process control. Analytical techniques may be included in the QbD paradigm. The AQbD methodology places a strong focus on having a thorough grasp of the workings of and factors influencing the analytical methods used in product development. Utilizing the numerous tools and approaches covered in the essay, the factors that have an impact on the output are discovered and thoroughly risk assessed before being optimized. A control strategy is implemented once the final procedure has been verified. To speed up the process of accepting this distinctive and successful methodology, worldwide standardization of QbD nomenclature and precise recommendations on application of the QbD approach in all domains of product development, including analytical techniques, are also required.

Keywords: *Quality, Quality by Design, Analytical QbD, MODR.*

INTRODUCTION

Quality-by-design (Qbd), pioneered by the FDA, has become a major pharmaceutical paradigm. Any entity seeking regulatory clearance as a drug must demonstrate safety, efficacy, and quality. To assure pharmaceutical product and system uniformity, "quality" has been developed rather than evaluated. Qbd starts with this idea. In ICH guideline Q8 (R2), "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" is QbD. It "means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely derived from performance of test batches," according to Janet Woodcock (2004).QbD emphasizes process design and process performance in connection to product performance. Process knowledge informs continuous improvement, a critical plan element. A "desired state" with "regulatory flexibility" emphasizes scientific understanding, excellent design, performance demonstration, Quality Risk Assessment (QRM), Design of Experiments (DoE), Process Analytical Technology (PAT) tools, ongoing learning, and life-cycle management. Figure 1 illustrates QbD-based progression creation.[1-5]

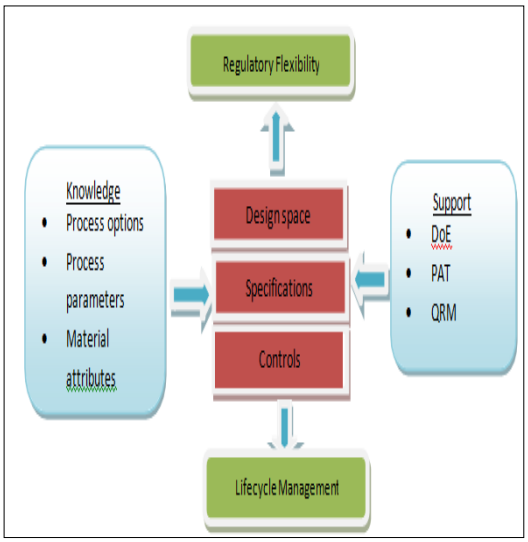

Figure 1: Building blocks of Quality by Design (QbD);

Key terms: QRM: Quality Risk Management; DoE: Design of Experiments; PAT: Process Analytical Technology

Table 1: Difference between Conventional approach and Qbd

approach

Conventional approach	QBD approach
Quality assured by testing and inspection	Quality is built into the product and process by design and scientific approach
Includes only data for submission	Submission with product knowledge and process understanding
Specifications are based on batch history	Specifications are based on product performance requirements
Process is frozen, discourages changes	Flexible process with design space, allows continuous improvement
Focuses on reproducibility ignores variation	Focuses on robustness which understands control variation

Benefits of QBD: [6-8]

- • Flexibility in the examination of API, dosage form impurities, stability samples, and biological sample metabolites.
- • A decrease in analytical attribute variability to increase the method's robustness.
- • Get rid of batch errors.
- • Reduce expensive investigations and deviations.
- • Prevent issues with regulatory compliance.
- • Science is excellent with QbD.
- • Improved development choices.
- • Giving technical workers more authority.
- • Easy transition of the technique to the production level.
- • Historical context
- • Although Quality by Design (QbD) is not particularly new, it has been seen as a new paradigm in the pharmaceutical sector. Table 2 provides the history.[9-11]

Table 2: History of QBD

Year	Activities
1950	Operation windows
1970	QBD created by Joseph M Juran
Sep 2002	QBD concept integrated by USFDA in cGMP
Sep 2004	USFDA release final report in "Pharmaceutical cGMP"
Sep 2004	USFDA Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
Nov 2009	ICH: Q8(R2) Pharmaceutical Development
Nov 2005	ICH: Q9 Quality Risk Management
Jun 2008	ICH: Q10 Pharmaceutical Quality System

KEY ASPECTS OF ANALYTICAL QBD

Analytical target profile

ATP is like QbD's QTPP. Method development uses ATP, according to ICH Q8 R(2). It lists technique requirements to

be measured. "ATP is a statement that defines the method's purpose which is used to drive method selection, design, and development activities," PhRMA and EFPIA said recently.[12]

General ATP for analytical procedures is as follows:[13-14]

Selection of the target analytes (API and impurities), selection of the technique (HPLC, GC, HPTLC, Ion Chromatography, chiral HPLC, etc.), and

• The choice of the method's requirements (assay, impurity profile, or residual solvents).

• Risk assessment and Critical Quality Attributes

CQA (Critical Quality Attributes)

Analytical methodology CQA includes method features and parameters. Analytical methods have different CQAs. HPLC CQA includes mobile phase buffer, pH, diluent, column choice, organic modifier, and elution procedure. Gas flow, oven program, injection temperature, sample diluent, and concentration are GC procedures CQA. CQA includes HPTLC plates, mobile phases, injection concentrations and volumes, plate development periods, color development reagents, and detection methods. Solubility, pH, charged functional groups, polarity, boiling point, and solution stability may characterize CQA for analytical procedures.

Risk Assessment

After identifying the technique, AQbD conducts extensive risk assessments of method variability elements such analyst methodologies, instrument design, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions. Analytical QbD requires risk assessment before method transfer and throughout the product life cycle. Traditional method development tested the method after transfer.

"It is systematic process for the assessment, control, communication and review of quality risks across the product lifecycle," according to the ICHQ9 standard.[15] This stage is essential for technique reliability.

ICH Q9 recommends risk identification, analysis, and evaluation for risk assessment.16 Fig 2: Risk Assessment steps.

Risk Identification is essential for identifying and prioritizing hazards. Risks include instrument functioning, reagent properties, cycle time, etc. Always have a backup plan. Checklists and flowcharts highlight risk variables. Risk Analysis follows. This phase uses Ishikawa Fishbone Diagram and CNX. Cause and Effect or Ishikawa Fishbone diagrams categorize hazards by source. CNX, which stands for high risk, noise, and experimental factors, is another instrument. This method categorizes risk variables as:

High Risk Factors – for instance, sample preparation techniques. During the method development process, they will be corrected.

Noise Factors: An MSA research will be conducted on them. done using variability plots and a staggered cross-nested research design. Robustness testing is applied to these elements.

Experimental Factors: Instrumentation and operations. Ruggedness testing determines range. FMEA and matrix designs evaluate risk in the third stage.[18]

Control Strategy

Controls for all conceivable variations ensure that ATP requirements are satisfied throughout analytical method transfer and everyday usage. Continuous CMA or system suitability parameter monitoring achieves this. Control approach might alter during method development.[19]

Lifecycle Management

Method validation, method verification, and method transfer are the main exercises that verify the method is suitable for its intended application even after passing through all the QbD components for a specific analytical method have been completed. Taking all of this into account, we can refer to it as "lifecycle management of analytical procedure," which begins with ATP establishment and lasts until the technique is in operation. Performance qualification, such as precision investigation on the site of regular usage, is primarily focused on the subsequent confirmation with regard to ATP. Activities that are included in continuous verification provide the confidence that the method is under control throughout its lifespan.

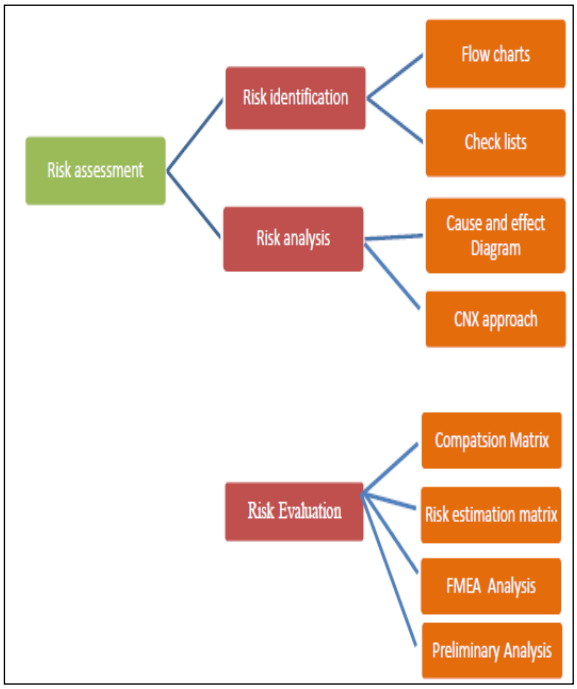

Fig 2: A sequence of steps involved in Risk Assessment and the various tools involved in the process as mentioned in ICHQ9 Guidelines.

Tools of QBD:[20]

Design of Experiments

Method operable design region (MODR) may be formed in the method development phase in accordance with the need of ICHQ8 rules, about "design space" in product development, which might be a source for reliable and affordable methods. The crucial method input variable's operating range, or MODR, is what delivers outcomes that consistently satisfy the ATP's objectives. It is comparable to CQAs. Without having to resubmit to the FDA, MODR enables flexibility in a number of input method parameters to provide predicted method performance criteria and method response. It is based on a scientific, risk-based, and multivariate methodology to assess the impact of several variables on the effectiveness of the procedure. FDA has advised that MODR be conducted in conjunction with method validation. Once this has been established, the proper method controls may be implemented, and method validation can be done. Numerous analytical studies have been published that use response surface methods, factorial or fractional factorial experimental designs, or both. However, the focus of their efforts was on creating mathematical models that would connect input variables (Xn) with output responses (Yn). DoE implementation during the method development phase necessitates a deep comprehension of input variable selection and output reaction. The following is a list of DoE in the AQbD technique.

Screening

Screening allows for the exclusion of qualitative input characteristics. It lists the different critical method parameters (CMP) that should be taken into account throughout the optimization studies. It also functions as a semi-optimization tool to show the degrees of CMA needed for optimization tests. Table 4 displays the different tool and selecting methods.The CMP that has to be either regulated or

exposed to DOE approaches in MODR optimization should be separated out as a result of the screening studies.

Optimization

Quantitative metrics for crucial method in variables (i.e., CMP) may be introduced at this point either directly from risk assessment or through screening. It offers a foundation for understanding the scientific relationship between the amounts of input variables (CMP) and output responses, which will have a significant impact on the effectiveness of the approach and ATP.

Selection of DOE Tools

Many mathematical models may be derived during optimization.The amount of input variables, knowledge of regulated parameters, and scientific understanding of result-variable relationships should guide DoE tool selection. Statistical knowledge helps analyze the interaction and contribution of variables (Xn) in method replies (Yn) and pick optimal variables. Factorial design may be used to quantify the effects of all input variables and their interactions, then optimized by RSM. Taguchi technique may be employed with fewer experimental runs than factorial designs (50%, 25%, etc.), but interactions must be handled. Plackett-Burman techniques can study several input variables without interaction effects. Table 3 lists typical methods.

Table 4: Selection of DOE tools in analytical quality by design.

Design	Number of variables and usage	Advantage	Disadvantage
Full factorial design	Optimization/ 2-5 variables	Identifying the main and interaction effect without any confounding	Experimental runs increase with increase in number of variables
Fractional factorial design or Taguchi methods	Optimization/ and screening variables	Requiring lower number of experimental runs	Resolving cofounding effects of interactions is a difficult job
Plackett-Burman Method	Screening or identifying vital few factors from large number of variables	Requiring very few runs for large number of variables	It does not reveal interaction effect
Pseudo-Monte Carlo sampling (pseudorandom sampling) method	Quantitative risk analysis/ optimization	Behavior and changes to the model can be investigated with great ease and speed. This is preferred where exact calculation is possible	For nonconvex design spaces, this method of sampling can be more difficult to employ. Random numbers that can be produced from a random

			number generating alogrithm
Full factorial Design	Optimization/ 2-5 Variables	Identifying the main and interaction effect without any confounding	Experimental runs increase with increase in number of variables

Method Operable Design Region (MODR) and Surface Plots

Figure 3(a) shows MODR's 2D model contour plot. The contour plot is a 2D response graphic that shows how pH (x-axis) and % aqueous phase (y-axis) affect analyte retention time while controlling flow rate and other instrument parameters. DOE plan variables are coded as −1, −2, +1, and +2 on both axes. If the response is nonlinear and the input variable-method response relationship is curvy, this shape is acceptable. Mathematical models choose MODR from contours. Model validation utilizing experimental runs helps verify technique response prediction. Another simulation-based surface model that shows response change with variables is better for linear relationships. Fig. 3(b).

Model Validation

Before choosing contour or graph, the projected method response values must be checked by experimental run. Regression analysis validates the model statistically.

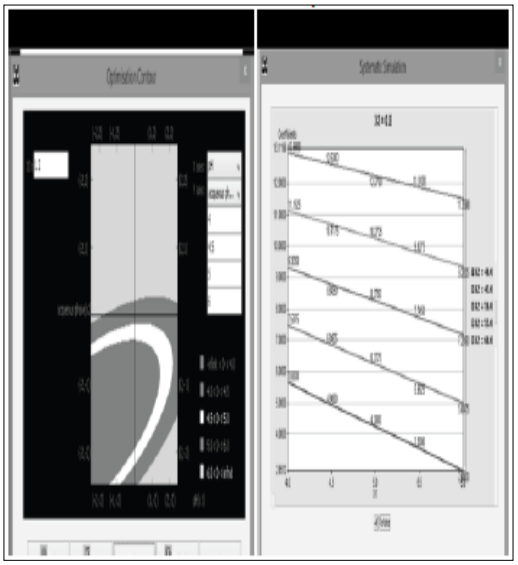

Figure 3: (a) Contour plot for MODR (retention time as method response). (b) Systematic simulation graph for retention time (y-axis) as method response at constant X3 (0.8 mL/min as flow rate) with change in pH (X1-x-axis).

Process analytical technology

Parallel analytical QbD development is advised for process analytical technology (PAT) system installation. PAT has two main components: comprehending the scientific and technical foundations of production and identifying product quality factors. "The desired state of pharmaceutical manufacturing is that product quality and performance are ensured through the design of effective and efficient manufacturing processes," the FDA draft guideline said, recommending continuous and real-time quality assurance. After understanding drug product component qualities, processing factors that govern them must be discovered. These variables must be identified multivariately. To improve PAT, pharmaceutical companies are using process knowledge and analytical control systems.

Risk Management Methodology[21]

- Quality Risk Management is "A

systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle". Based on past knowledge and primary experimental data, risk assessment systems may identify and level aspects (e.g., process, equipment, input materials) that may affect product quality. Design of experiments and mechanistic models may narrow the initial list of possible factors. To improve process knowledge, significant parameters might be explored via design of experiments, mathematical models, or mechanistic investigations.

The pharmaceutical business and regulators may analyze and manage risks using well-known risk management tools and/or internal processes such,

- Basic risk management facilitation methods (flowcharts,check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Applications of Quality By Design 22-23

Application to Analytical QBD

- Development of a robustmethod.
- Understand, reduce and control sources of variability.
- Applicable throughout the life cycle of the method.
- Regulatory flexibilityMovements within "Analytical Design Space" are not considereda change in method.

Application to Industry:

- Ensures better design of products with less problems in manufacturing.
- Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation.
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny.
- Allows for possible reduction in overall costs of manufacturing –less waste.
- Ensures less hassle during review – reduced deficiencies –quicker approvals.
- Improves interaction with FDA – deal on a science level instead of on a process level.
- Allows for continuous improvements in products and manufacturing process.

CONCLUSION

Pharmaceutical processes including drug development, formulations, analytical methods, and biopharmaceuticals have seen a rise in the significance of QbD. The key driver of QbD adoption is the need to comply with regulations. In the pharmaceutical sector, Analytical Quality by Design (AQbD) is crucial for assuring the quality of the final product. Understanding from product development to commercial manufacturing is the result of A QbD. The AQbD tools are the ATP, CQA, MODR, and Control Strategy with Risk Assessment, Method Validation, and Continuous Improvement. A QbD needs the necessary ATP, risk assessment, use of the suitable tools, and completion of the required amount of work within the proper time frames. For this strategy to be effective, the pharmaceutical sector must be unwavering in its commitment.

REFERENCES

1. International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use, Pharmaceutical Development Q8 (R2). ICH

harmonized tripartite guideline, Draft Step 4. 2008, 13-15.

2. Yu L. Pharmaceutical quality by design: Product and process development, understanding and control. Pharm Res. 25,2008, 781–791.

3. Lee SL, Raw AS, Yu L. Significance of drug substance physiochemical properties in regulatory quality by design. In Drugs and the Pharmaceutical Sciences 78 (Pre formulation in Solid Dosage Form Development), London: InformaHealthcare, 2008, 571–583.

4. Mhatre R, Rathore AS. Quality by design: An overview of the basic concepts. In Quality by design for biopharmaceuticals. New York: Wiley, 2009, 1–8.

5. Pritesh Dasare. Analytical Department, SPARC, Sun Pharmaceuticals Industries, Ltd, Baroda, [Accessed on: March 2, 2017].

6. Woodcock J. The concept of pharmaceutical quality. American Pharmaceutical Review, 7(6), 2004, 10–15.

7. Q10: Pharmaceutical Quality System, ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.

8. FDA Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool (Draft Guidance).

9. Snee RD. Status update: QbD. Pharm Process, 2013, 24-26.

10. Walrath I, Glessner C, Cheung A, Ressler D. The new gold standard: Pfizer's Quality by design approach to trial management. Pharm Exec, 2013, 48-52.

11. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nat Biotechnol, Jan; 27(1), 2009, 26-34.

12. F. G. Vogt, A. S. Kord, "Development of quality-by-design analytical methods," J. Pharm. Sci, vol.100, no. 3, 2011, 797–812.

13. M. Schweitzer, M. Pohl, M. Hanna-Brown et al., "Implications and opportunities of applying QbD principles to analytical measurements," Pharmaceutical Technology, vol. 34, no. 2, 2010, 52.

14. http://www.sepscience.com/Sectors/Pharma/Articles/559-

15. / The-Development-Phase-of-an-LC-Method-Using-QbD- Principles. [Accessed on: March 10, 2017].

16. Drug product and delivery, SSCI, Crystallization Expert, 2014, http://www.ssciinc.com/DrugSubstance/PATandPharmaceuticalQualityByDesign/tabid/86/Default.aspx[Accessed on: March 10, 2017].

17. Frederick, G.V., Alireza, S.K. "Development of quality-by- design analytical methods "Journal of Pharmceutical Sciences Volume 100, Issue 3, 2011, 797–812.

18. J.N. Sangshetti, M. Deshpande, Z. Zaheer, D.B. Shinde, R. Arote, Quality by design approach: Regulatory need, Arab. J. Chem., 2014.

19. B.P. Borman, P. Nethercote, M. Chatfield, D. Thompson, K. Truman, The Application of Quality by Design to Analytical Methods, 2007, 2.

20. USP Validation and Verification Expert Panel, LifecycleManagement of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure PerformanceVerification,http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/revisions/lifecycle_pdf.pdf. [Accessed on: March 5, 2017].

21. Ramalingam P, Kalva B, and Reddy Y, Analytical Quality by Design: A Tool for Regulatory Flexibility and Robust Analytics Hindawi Publishing Corporation International Journal of Analytical Chemistry Volume 2015, 9.

22. Ian House Process Understanding: for Scale-up and Manufacturing method of Active Ingredients, First edition, Wiley-VCH Ver lags GMb H&Co. KGaA (2011).

23. Tang Y., Quality by Design Approaches to Analytical Methods FDA Perspective, U.S. Food and drug Administration, 2011.

24. Gholve SB, Ajgunde RR, Bhusnure OG, Thonte SS, Analytical method development and validation by QbD approach – A review Pelagia Research Library, Der Pharmacia Sinica, 6(8), 2015, 18-24.