A DISCUSSION OF QUALITY-BY-DESIGN APPROACHES TO THE DEVELOPMENT OF ANALYTICAL METHODS

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ABSTRACT

QbD encompasses drug development. Drug development ensures quality. Quality by Design new medications. The FDA and most regulators are scrutinizing drug development data. Scientifically, risk-based, systematically, and aggressively approach these authorities, including the FDA. Industrial principles explain product development and manufacture, including quality rather than assessing it. QbD now uses analytical methodologies in product design and development. Product planners must create a desired product performance profile, target product profile, target product quality profile, and key quality characteristics (CQA) for quality by design. Pharmaceutical companies adopt Quality by Design. The EMA (European Medicines Agency) and ICH authorities globally embrace the idea. Industry calls them AQbD ideas.

Keywords: *Quality by Design, Analytical Quality By Design, Target Product Profile, Target Product Quality Profile, Analytical Target Profile.*

INTRODUCTION

Drug quality affects public health, hence competent regulatory agencies control pharmaceutical manufacture. Regulate drug quality. Pharmaceutical companies aim to meet standards. Quality means satisfying customers. Quality, reliability, pricing, and quickness satisfy customers. Quality derives from the Latin term 'qualis', meaning 'of what type'. Drug quality important. Pharmaceutical quality meets standards.

Pharmaceutical development and production experience shape design space, requirements, and manufacturing controls. Drug development data may aid risk management. Product development should include patient demands and use. Product and company development differ. The proposal must describe strategic adjustments. Candidates may build products empirically and systematically. FDA-pharmaceutical quality by design argument employs numerous key words. Quality by design and its name remain ambiguous, according to industry opinions. Pharmaceutical businesses employed off-line analysis and product standards before QbD. Scaling difficulties emerged. Revalidation and approvals were more expensive. QbD installation changes everything. The pharmaceutical industry has a systematic development plan with goals. THIS PAPER EXPLAINS ANDA QBD.

Analytical methods create products. A reliable analytical method maintains drug purity and medical quality throughout product development. The final quality control results and other batch data decide a product's market release, thus the analytical technique utilized for commercial product manufacturing must be time-saving, reliable, and accurate. Analytical methods measure material physical, chemical, physicochemical, and biological properties. HPLC, GC, HPTLC, and SFC are popular because they offer several benefits over non-chromatographic

procedures. Durable and requiring fewer samples. Automation decreases mistakes.

Analytical chemists develop precise methods. Analytical chemistry has two technique development strategies. Trial-and-error optimizes one parameter at a time (OFAT). This method's instrumental variables are always unreliable. Analytical approaches like OFAT are dangerous and need revalidation after method transfer or when establishing alternative methods, which increases methodology expense. AQbD procedures are based on science. Method selection begins with product quality and risk evaluation, next method parameter and expected method results, and finally a robust and economically feasible strategy. Input factors affect approach behavior and outcomes in AQbD's DoE. Analytical method development should use AQbD to reduce OOS, OOT, and OOC results and gain regulatory flexibility. This method examines chromatographic process management and monitoring aspects.

Advantages of QbD can be summarized as,

- Patient safety and product efficacy are focused.
- Scientific understanding of pharmaceutical process and methods is done.
- It involves product design and process development.
- Science based risk assessment is carried.
- Critical quality attributes are identified and their effect on final quality of product is analyzed.
- It offers robust method or process.
- Business benefits are also driving force to adopt QbD.

List of regulatory Guidelines/Activities:

Complex manufacturing procedures like airplane production need product quality design or construction. In August 2002, USFDA issued a guideline paper called "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" for pharmaceutical development. Since then, several pharmaceutical QbD regulatory recommendations have been issued, as shown in Table. Other pharmaceutical quality-improvement organizations also do QbD-related tasks.

Regulatory guidelines or other QbD related activities

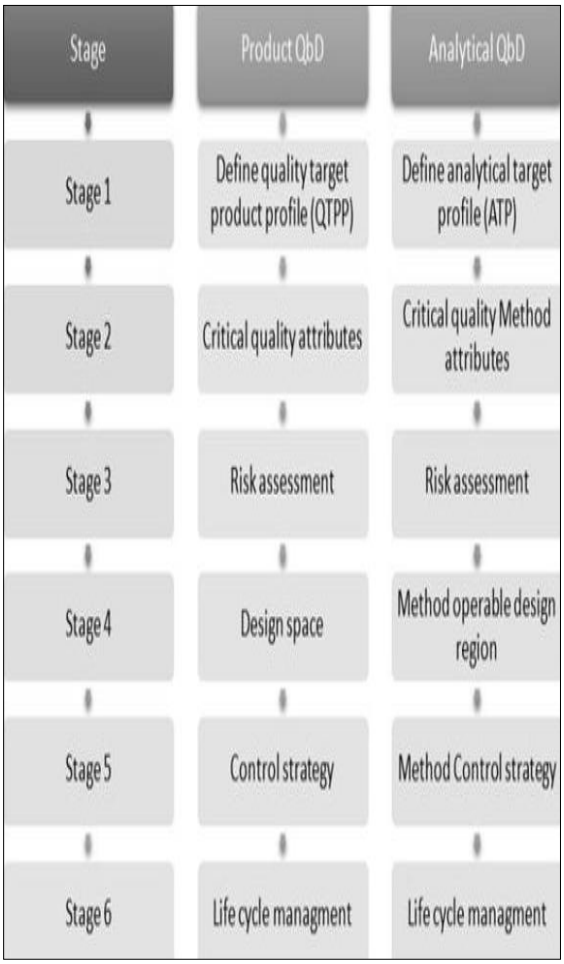

Figure : Regulatory perspective of QbD vs AQbD.

Steps involved in QbD:

Development of new molecular entity

- Preclinical study
- Nonclinical study

- Clinical Study
- Scale up
- Submission for market Approval

Manufacturing

- Design Space
- Process Analytical Technology
- Real time Quality Control

Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance

Seven steps of QbD startup plan:

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your "Project Assurance" advisor.

Key aspects of QbD:

Target Product Quality Profile (TPQP):

Drug development strategy begins with the Target Product Quality Profile (TPQP). TPP usage in development planning, clinical and commercial decision making, regulatory agency engagement, and risk management has increased lately.

Target Product Profile (TPP):

TPP summarizes the drug's key characteristics and usage. These features set medication development program goals. TPP helps the lead development team plan medicinal chemistry, pharmacology, toxicology, formulation, etc. It optimizes a medication candidate, helps organizations make decisions, designs clinical research schedules, and communicates with regulators. TPP concludes with the drug's pharmacology, indications, use, methods of administration, and side effects. It connects medication development to labeling.

Quality Target Product Profile (QTPP):

The drug product must have these qualities to reliably provide the labeled therapeutic benefit. Identity, assay, dose form, purity, and stability. Formulation scientists use the QTPP to plan high-quality product formulations. QTTP underpins product development.

QTPP is a projected summary of drug product quality parameters that should be met to assure safety and effectiveness. TPP usage in development planning, clinical and commercial decision making, regulatory agency engagement, and risk management has increased lately. The TPP is crucial to drug research and development:

1. Effective optimization of a drug candidate
2. Decision-making within an organization
3. Design of clinical research strategies, and
4. Constructive communication with regulatory authorities.
5. The TPQP guides formulation scientists to establish formulation strategies and it will keep the formulation effort to be focused and efficient.

Elements of Analytical QbD:

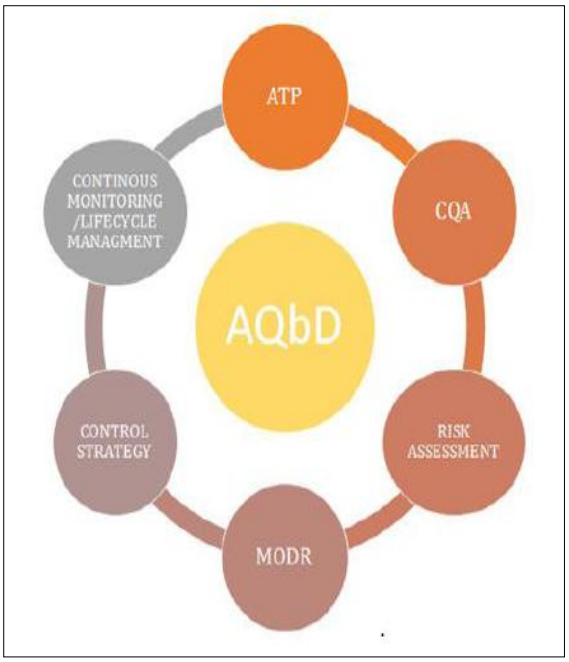

Figure : Elements of Analytical QbD.

AQbD/QbD comprises of all elements of pharmaceutical development described in ICH Q8 depicted in above Figure.

Analytical target profile:

ICH Q8R recommends ATP for method development. Chromatography quantifies and identifies drug, impurity, and degradant. Impurity CQA. Knowing past synthesis, manufacturing, and impurity paths can help with traces. ICH guidelines require accuracy, precision, robustness, durability, etc. Using QbD or traditional methods, record compound solubility, pKa, pH, UV chromophore, and stability.

Method Design:

Material availability and experimental conditions influence method design. Provides reagents. Consider geography. Designing and testing instruments. HPLC method discovery. pH, temperature, columns, and buffers were examined.

Software creates data from experimental values. Then the database forecasts the consequences of numerous chromatographic parameters. Predictive software avoids experimentation. Resolution, runtime, and design response. Saves time and money. Software supports technique changes. HPLC, LC, or Raman are among the analytical methods used in method design. Selecting the best method.

DoE's MDS. It teaches current risk assessment methodologies and allows parameter customization. ICH-based method design formalizes validation. Experiment with numerous components at particular values. Experimental designs:

- Full factorial,
- Fractional factorial,
- Plackett–Burman designs

CQA (Critical Quality Attributes):

ICH Q8 defines CQA as a physical, chemical, biological, or microbiological characteristic or feature within an acceptable limit, range, or distribution to ensure product quality. Analytical method CQA features and parameters. Analysis affects CQA.

HPLC buffers, mobile phase pH, diluent, column selection, organic modifier, and elution method CQA.

GC Oven, program, injection, gas flow, sample diluent, and concentration are CQA.

HPTLC TLC plate, mobile phase, injection concentration and volume, plate development time, color development reagent, and detection methods comprise CQA.

CQA may leverage medication component and contaminant features such polarity, charged functional groups, solubility, pH value, boiling point, and solution stability to construct analytical techniques.

Before method development, product quality and safety are addressed. Knowing product and process simplifies CQA. The HPLC technique for a drug component with an impurity that might affect quality and safety must be devised. Quantifying

product quality shows safety, specification, intermediate specification, and process control effectiveness.

Risk Assessment:

"It is systematic process for the assessment, control, communication and review of quality risks across the product lifecycle," according to the ICH Q9 guideline. This stage is essential for technique reliability. After identifying the methodology, AQbD conducts extensive risk assessments of analyst methodologies, instrument design, measurement and method parameters, sample characteristics, sample preparation, and environmental circumstances that may affect method variability.

It links input process variable to CQA. Risk assessment tools include,

1. Ishikawa or fishbone diagram,
2. Failure mode effect analysis (FMEA),
3. Pareto analysis.

An Ishikawa or fishbone diagram lists all variables that might affect a CQA, such as raw materials, instrumental factors, and environmental factors. A FMEA may then rank variables by risk (i.e., likelihood, severity, and delectability) and pick process parameters with higher risks for subsequent research to better understand their influence on CQAs.

Chromatographic technique development focuses on chemical separation and identification. Risk assessment emphasizes robustness in QbD. Risk assessment includes small procedure parameter changes such reagents, instruments, analyst, labs, days, temperature, and humidity. DoE and MSA can analyze data. If the main method fails, a backup is risk-assessed until a viable technique is found. The optimal approach is chosen by comparing robustness and roughness if both methods have benefits.

Principles of quality risk management are:

- Scientific knowledge based evaluation of the risk to quality which eventually links to the protection of the patient.
- Adequate effort should be taken; formality and documentation of the quality risk management process should be done with the level of risk involved.

Analytical QbD requires risk assessment before method transfer and throughout the product life cycle. Traditional method development tested the method after transfer. ICH Q9 recommends risk identification, analysis, and evaluation for risk assessment. Risk factors are categorized as follows:

- **High Risk Factors:** e.g. Sample preparation methodology. These are to be fixed during the Method Development process.
- **Noise Factors:** These are subjected to an MSA study. It can be done through staggered cross nested study design and variability plots, ANOVA etc. These factors are subjected to robustness testing.

Experimental Factors: e.g. Operation and instrumentation. Ruggedness testing determines range. FMEA and matrix designs evaluate risk in the third stage.

HPLC impurity profiling using staggered cross nested design and Karl Fisher Titration (KFT) employed System Analysis (MSA). Robustness experiments were designed.

Risk assessments: ICH Q9 lists risk assessment methods:

- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);

- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

Method qualification

Method qualification follows method design, taking into account analytical target profile (ATP) and development risk. Method qualifying includes equipment qualification. MIQ, MPQ, and MPQ are its subcategories.

HPLC instruments demonstrate instrumental qualification. HPLC chromatographic method development might be qualified.

Secure Data Storage, Backup, and Archive

When required, secure data handling, such as storage, backup, and archiving should be tested at the user site according to written procedures.

Instrument Functions Tests

Test critical instrument functionalities to ensure manufacturer and user expectations are met. According to the instrument's purpose, the user should test key parameters. These settings may be specified using vendor information. Parameters should be tested. These tests ensure that the instrument satisfies vendor and user criteria.

Instrument OQ testing depends on its intended use. No instrument or application-specific OQ tests are offered. However, these HPLC tests are examples of OQ testing:

- Pump flow rate
- Gradient linearity
- Detector wavelength accuracy
- Detector linearity
- Column oven temperature
- Peak area precision
- Peak retention time precision

Performance Qualification (PQ)

After the IQ and OQ have been performed, the instrument's continued suitability for its intended use is proved through performance qualification. The PQ phase includes these parameters:

Performance Checks

Test the instrument's performance for its intended usage. PQ testing generally simulate the instrument's on-site use. Some tests may mimic OQ, although their outcomes may be specified differently if needed. PQ testing are frequently done on operational instruments. Thus, OQ standards are stricter than PQ specifications. However, PQ test user requirements should ensure instrument functionality for intended applications.

Development of experimental design

Experimental design is the multidimensional mixing and interaction of quality-ensuring input elements (e.g., material characteristics) and process parameters. The applicant offers ICH Q8 (R2) regulatory clearance design space. CAPD and process simulation help pharmaceutical developers enhance manufacturing processes.

Design space ensures product quality. Unit activities may employ many design areas. Placket–Burman, Taguchi, Surface Design, Full and fractional factorial designs are mathematical experiment designs. A complete factorial experiment examined how formulation factors impact tablet pharmacological attributes. Binder and disintegrant concentration, crushing resistance, and drug release were

independent variables. Multidisciplinary strategies improve production in previously permitted areas to decrease marketing variation. Risk-based strategies emphasize timely quality control above final product testing.

Designing and implementing control strategy

Control strategy is needed to maintain material and process constraints. Production controls material and parameters to ensure repeatability. Design space should include control space. Scaling up involves trial and error. Control is needed since scale-up operations change parameters but not quality qualities. QbD tracks repeatability and robustness. Process capability index measures reproducibility.

Process capability index (CpK) = Upper limit of specification - lower limit of specification / 6standard deviation

Establishing a control plan is crucial to ATP aims of routinely achieving method performance. A designed set of controls reduces process variability. Data determines strategy. Control strategy data comes from method development and verification. Control risk factors. High-risk indicators are prioritized. If the risk is minimal and controllable, the method control approach may be designed, which usually involves a system suitability assessment and periodic management to ensure the method provides the desired method characteristics.

Control space, an upper and lower limit for raw material or a process where parameters and material are frequently regulated to ensure product quality, should be within the design space. (Fig. 5). Robust control space is smaller than design space. QbD technique is proactive in the first phases and identifies prospective qualities that might generate out of range results and impair quality. Design space examines intentional variances.

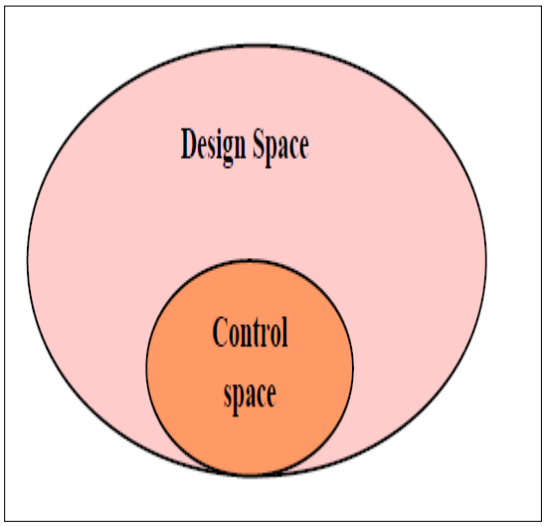

Figure : Control space within the design space.

Lifecycle Management

technique validation, verification, and transfer are essential processes in AQbD for an analytical technique. Lifecycle management of analytical process begins with ATP establishment and continues till techniques are used. Performance qualification—e.g., precision study during regular use—focuses on ATP confirmation. Continuous verification ensures method control throughout its lifespan.

Companies may innovate to enhance product quality throughout the lifespan. Monitoring process performance ensures quality consistency. Routine manufacturing provides method/process development expertise.

Application of QbD in analytical methods of measurement

Using science and risk assessment, QbD means the appropriate analysis at the right moment. Pharmaceutical companies are using QbD because it develops durable

and resilient methods that conform with ICH guidelines. This methodology allows method improvement. Although not all pharmaceutical companies employ it, regulatory authorities may require it. Due to its advantages and legal compliance, companies may embrace this approach voluntarily. PhRMA, ATG, and EFPIA have proposed implementing QbD to analytical methods simultaneously. Analytical procedures using QbD include,

- Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
- Hyphenated technique like LC–MS.
- Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis.
- Karl Fischer titration for determination of moisture content.
- Vibrational spectroscopy for identification and quantification of compounds e.g. UV method.
- Analysis of genotoxic impurity.
- Dissolution studies.
- To biopharmaceutical processes.

Potential benefits of adopting QbD for analytical method

1. Scientific understanding of pharmaceutical process and method.
2. It provides a space for invention of new techniques by continuous improvement throughout life cycle.
3. Critical quality attributes are identified and their effect on final quality of product is analyzed.
4. It provides required design space for development.
5. Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples.
6. Reduction in variability in analytical attributes for improving the method robustness.
7. Minimize deviations and costly investigations.
8. Smooth process of method transfer to the production level.
9. It provides greater compliance with regulatory authorities.

Literature reports of application QbD or elements of QbD to analytical method

Dennis Asberg envisions a regulatory-approved analytical QC approach that can be improved with small modifications outside the design space, which is now impossible. Same-mATP HPLC-UHPLC shows this. A method upgrade permits small measurement principle modifications outside the MODR without regulatory monitoring. A pre-UHPLC HPLC-based QC case study supports the notion. The same measurement approach applies the SST and failure modes beyond the MODR. Alifiya S. Rajkotwala designed and validated a thorough scientific and risk-based HPLC technique for Piracetam API analysis utilizing quality by design. RP-HPLC mobile phase and pH scouting are great experimental designs. Methanol-dissolved piracetam reached 205 nm absorption. Software designers 10.0 modified chromatography: column C18, mobile phase buffer (pH 6.5): Acetonitrile+0.1% TEA (80:20), flow rate 1 ml/min. 20–70 µg/ml linear (R2=0.998). precision, ruggedness, and robustness were acceptable (<1% system accuracy and 2% other parameters). Chromatography didn't co-elute piracetam. Quality control labs test piracetam.

BV Girish This QbD-based RP-UPLC method separated and quantified Dimenhydrinate pollutants in oral

disintegrating tablets.Analytical goals. Gradient run employs XSelect HSS T3 (100*2.1mm, 1.8 µm) chromatographic column with Mobile phases A (65:35) and B (5:95). 2µl, 225nm, 30oC. DOE assessed gradient and mobile phase composition. Gradient steepness, mobile phase A and B acetonitrile and methanol percentages, and their interactions affected CQA. Technique space CCD statistics model. QbD-compliant technique was tested for specificity, linearity, accuracy, repeatability, range, detection limit, and quantitation. Forced degradation showed method stability.

Monika Jadhav developed tablet propafenone hydrochloride estimate chromatographic and spectrophotometric procedures using QbD and ICH Q8 (R2) criteria. Ishikawa diagrams altered QbD. Principal component analysis and observation established important parameters. HPTLC method critical parameters include solvent methanol, mode of detection absorbance, precoated aluminium-backed TLC plate (10 cm × 10 cm), wavelength: 250 nm, saturation time: 20 min, band length: 8 mm, solvent front: 70 mm, volume of mobile phase: 5 mL, type of chamber: 10 cm × 10 cm, scanning time: 10 min, and mobile phase methanol: ethyl acetate: triethylamine (1.5: 3.5: 0.4 v/v/v). Zero-order spectrophotometric technique suggested key parameters were solvent methanol, sample preparation tablet, wavelength: 247.4 nm, slit width: 1.0, scan speed medium, and sampling interval: 0.2. The following methods were confirmed by ICH Q2 (R1). Tablet propafenone hydrochloride analysis may employ advanced procedures.

Problems in adoption of QbD

1. Internal unwillingness in company
2. Lack of belief in a business case. It is assumed that QbD would require more time to file generic products or that the amount of clinical trials necessary to implement QbD for drug substance production
3. Lack of technology to implement.
4. Alignment with third parties. It is difficult to manage a multipart supply chain that includes both suppliers and contract manufacturers.
5. Inconsistent treatment of QbD across FDA. It is believed that FDA may not review filings in a consistent manner.
6. Lack of concrete guidance for industry. Companies wanted clarification from FDA on matters such as acceptable methods, criteria to select critical quality attributes, standards by which to judge adequacy of controls, and criteria for analytical method substitution.
7. Regulators not ready to handle QbD applications.
8. Presented regulatory benefits does not inspire to follow QbD
9. Misalignment of international regulatory bodies.

CONCLUSION

Pharmacists and regulators prioritize quality since drugs may save or kill. Patients must trust drugmakers. Change pharmaceutical quality management. Other sectors have developed more advanced and cost-effective quality procedures. Pharmaceutical quality management requires design quality. Q8, Q9, and Q10 support quality by design. Quality by Design lets the pharmaceutical industry employ existing quality management approaches for cheaper manufacturing and quality. QbD fosters creativity and excellence. QbD requires a contemporary quality system. Quality through design improves pharmaceutical quality. Analytical procedures need QbD because

instrument settings, sample attributes, method parameters, and calibration models affect results. QbD analytical technology development and validation assure pharmaceutical product quality. AQbD develops products using commercial manufacturing experience. Quality by Design (QbD) improves formulation and process development process understanding and risk detection and management. The technique enhances method proficiency, minimizes variability, trials, cost, and time, and notifies users about the method's severe constraints, which may lead to method failures and alternatives.

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