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Analytical Quality by Design – A Legitimate Paradigm for Pharmaceutical Analytical Method Development and Validation

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ABSTRACT. The apprehension and criticism on the quality and reliability of pharmaceutical products has augmented substantially, ensuing the regulatory bodies avowing the necessity of systematic principles for drug development. ICH instituted series of guidelines such as Q8, Q9, Q10 and Q11, all accentuating on implementation of systematic approaches of Quality by design (QBD) and Process Analytical Techniques (PAT). Quality by design has earned plentiful civility by formulation developers, the approach with sound scientific knowledge and early risk assessment is been accepted as an integral and imperative part of dosage form development, relishing the benefits of risk assessments on early stage and design space on the latter stage of product life cycle. However, the idea, reference, guidance and convention of practicing QBD in analytical discipline is limited, this article pronounces the ideologies and methodology of practising analytical QBD (AQBD) in analytical method development, dissolution test development and stability testing and validation design. The milestones of QBD such as Critical material attributes (CMA), Quality target product profile (QTPP), Critical quality attributes (CQA), Critical method parameters (CMP) and guidance for effective Design of experiments (DOE) differing from the conventional one factor at a time (OFAT) methodology are well explained. The software resources available for designing and interpretation of experiments, the statistical outcomes, its significance in establishing the control strategy and design space are well explained.

Introduction. The quality issue in pharmaceutical industries has become a very serious and domineering topic with China, Mexico, Canada and India rank in the first four places among the countries that received warning letters and import alerts from US FDA. Serious measures have been taken by pharma companies across world to put in more quality control measures in place. The manufacturing of pharmaceutical products used for achieving desired therapeutic aids for treatment of diverse ailments are considered as highly regulated since the past few decades. Poor manufacturing standards and their quality is being a worry for the industries and the regulatory agencies despite of the continuous contribution by the pharmaceutical industries in new drug discovery and innovations. The need for systematic approaches has been fingered mandatory both by the regulatory agencies and the manufactures. An article in, the wall street journal on September 2002 was an eye opener for the federal agencies on systematic approaches for drug manufacturing and quality control which compared the manufacturing standards of pharmaceutical industries with chips and laundry soap makers stated that the pharmaceutical industries are far behind in the quality aspects than the chips and soap makers [1].

The inevitable name “Juran”. Wherever there is a conversation on quality the name Juran is inevitable. Joseph M. Juran who have been called as the “father” of quality, a quality “guru” is a Romanian immigrant became the world well known expert in quality control has extended the philosophies of quality from the ancient conventional statistical practice to the todays so called quality management [2]. Juran is the man behind the quality of Japanese, suggests the need of managerial processes that focus on quality. The three managerial processes explained by Juran comprises of

quality planning, quality control and quality improvement, these three processes are combined called as Juran's Trilogy [3]. The term Quality by design was first coined by Juran in his well-known publishing "Juran on Quality by design". Juran supposed that quality could be strategic, and that most quality problems relate to the way in which quality was strategized [4,5].

Definition and Principle. QbD a systematic approach, begins with predefined aims, and smearing systematic understanding and risk managing approaches for drug development [6,7].

Quality by design is a methodical approach, braced by an extensive variety of statistical, economic, planning, psychological and other tools for risk assessment, establishing a design space, control strategy and recurrent improvement to upsurge method robustness, to close the quality gaps and shut down the hatchery of failures [5].

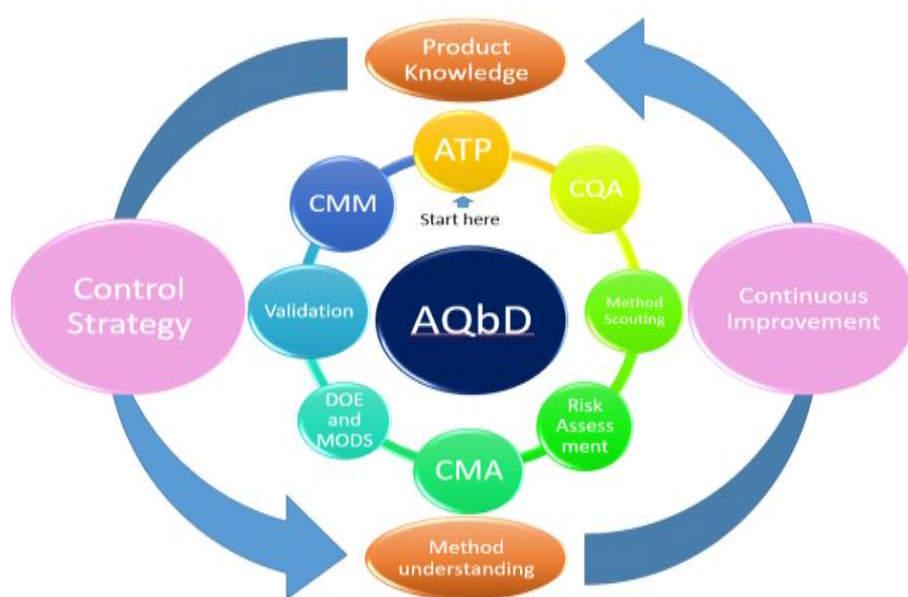


Fig. 1. AQbD lifecycle.

Table 1. Conventional approach versus QbD approach.

Parameter	Traditional	AQbD
Approach	Based on trial, error and understanding approach	Based on systematic approach
Performance	Performance is guaranteed by product testing and validation	Quality is constructed in the Robustness and reproducibility of the method built in method development stage
FDA submission	Including only data for submission	Submission with product knowledge and assuring by analytical target profile
Reliability	Method are based on batch trail and validation report.	Based on method performance to ATP criteria
Method	Method is frozen and discourages changes	Method flexibility with MODR and allowing continuous improvement
Targeted response	Focusing on reproducibility, ignoring variation	Focus on robust and cost effective method
Advantage	Limited and simple	Replacing the need of revalidation and minimizing OOT and OOS

Benefits of implementing AQbD. Thorough understanding of attributes of the method. Enhanced knowledge sharing, development of high performance methods, dynamic control strategy leads to greater operative elasticity, efficient regulatory oversight, regulatory filing based on science and automatus rationale, saves significant resources as testing is only real-time, improved time to reach market, reduced consumer-generic scepticism, excellent returns on investment, limited product recalls and rejects, decreased post-approval changes.

Regulatory prospective on QbD. The systemic approach to process and product design (QbD) concept was first accepted by FDA in 2004 and its view was published in ‘pharmaceutical cGMPs for 21st century – a risk based approach’[8]. In the same year FDA printed “Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance” in 2004. The outline is created on procedure thoughtful to facilitate novelty and risk-based regulatory inferences by manufacturer and the Agency [9]. Subsequent to that in 2005 FDA requested the New drug applicants were requested to submit chemistry manufacturing control (CMC) demonstrating Qbd.[10] The guidelines for QbD aspects were well explained by regulatory bodies through ICH guidelines such as Q8, Q9, Q10 explains about pharmaceutical development, quality risk assessment and pharmaceutical quality systems respectively explains the requirements and prospect of regulatory agencies on quality of product.

AQbD and QbD. There are enough lights thrown on formulation development QBD point of view whereas either illustrations or guidance available for analytical QBD is very limited. The QBD philosophy in pharmaceutical formulation development emphasis on developing quality products with robust process techniques, the analytical QBD ensures robust analytical methods developed during product development and the unique quality of the product was ensured throughout the shelf life. Analytical QBD begins with predefined objectives. The elements of AQBD are Quality target method profile (QTMP), Identifying the critical method attributes (CMVs), affecting the Critical analytical attributes (CAAs) for accomplishing enhanced method performance such as robustness, ruggedness and leaving a scope for continual improvement within the design space. AQbd decreases the variability and enables to take timely decision and in turn taking control over the product information. This provides confidence on the product quality and facilitates the analysis of raw materials, finished products, stability samples, biological samples and to benefitted beyond the conventional ICH procedures. AQbD gets on board with Formulation QbD upon quality risk assessment studies like Basic risk management simplification methods (flowcharts, check sheets, Supporting statistical tools etc.), Failure Mode Effects Analysis (FMEA), Failure Mode, Effects and Criticality Analysis (FMECA), Hazard Analysis and Critical Control Points (HACCP), Preliminary Hazard Analysis (PHA), Hazard Operability Analysis (HAZOP), Fault Tree Analysis (FTA), Risk ranking and filtering and Design of Experiments (DOE) guided multi factor screening and design space design studies for ensuring the method performance [11,12,13].

Elements of QBD. Employment of AQbD rest on the target measurement which encompasses the product dossier in the form of ATP (analytical target profile, is the correspondent of QTPP in process design) and CQA (Critical quality attributes), followed by considerate on selection of suitable analytical technique, risk assessment for method and material variables, method scouting using DoE, generate method operable design space (MODS) and validation process for model, control strategy and continual improvement focussing the life cycle management [14,15].

Analytical target profile (ATP). ATP is the equivalent of QTPP in process design, it the foremost step in AQbD, it's the goal setting process in the approach of developing the method. The ATP says about the set of attributes defining which moiety will be quantified, in which product, by what technique, over what concentration range along with the desired performance characteristics, The Specifications, acceptance limits should be connected to the proposed purpose of the analytical method [16]. Various aspects of methods with respect to HPLC/GC method such as phases selection, instrument requirement, sample characteristics, standard and sample preparation, procedural requirements such as sonication, centrifugation, mechanical shaking, diluent selection based on

solubility and pH of mobile phase/ diluent considering the pKa of the analyte shall be targeted based on the product and molecular known facts [17]. The literature survey performed as a primary task in conventional method development is also an integral part of ATP in AQbD. The method performance expectations such as precision, accuracy, range, detection limit, quantification limit, specificity, linearity, robustness, and ruggedness shall be assumed as predefined targets. A comprehensive knowledge of the envisioned purpose of the method must be developed from the understanding of moiety, its degradant, process impurities and the degradation pathways, sensitivity of drug to acid, base, oxidation, light, temperature, humidity and finally the critical quality attributes(CQAs)for the product [18].

Table 2. Formulation QbD Vs Analytical QbD [12].

Steps	Formulation Qbd/ FBD		Analytical QbD	
	Element	Objective	Element	Objective
1	Quality target profile (QTPP)	Define the type of drug delivery system, dosage form, dosage design, pharmacokinetics, stability expectations of formulation	Analytical Quality profile	Defines what to quantify and how to quantify.
2	Critical quality attributes (CQA)	Define the physical attributes, identification, Assay, Dissolution, Impurity profile requirements and other quality expectations	Critical quality attributes (CQA)	Separation, identification, accuracy, precision, robustness, ruggedness requirements
3	Critical process parameters (CPP)	Identifying the process parameters which could have impact on quality such as critical load level, agitation level, temperature, pH	Critical Method attributes (CMA)	Identifying method parameters which could have impact on the performance of the method, such as buffer pH, column temperature, injection volume, organic concentration etc.,
4	Critical Material attributes (CMC)	Evaluating the criticality type and grade of raw materials used in formulation	Critical Material attributes (CMC)	Evaluating the reagents, reagent grades and concentrations used in the analysis.
5	Design of Experiments (DOE)	Nested or factorial design to identify a centre process and create a design space	Design of Experiments (DOE)	Nested or factorial design identify a centre method and create a method design space
6	Process validation	Establishing practical proof that a process is reliably bringing quality products	Method validation	Establishing practical proof that the method is reliably bringing quality results
7	Control Strategy	Ensuring the product production with desired quality	Control Strategy	Ensuring the method performance with accepted results

Table 3. ATP for API and Finished dosage forms [15].

ATP elements	Target	Justification
Target sample	Active ingredient or Finished drug product	Developing a analytical method to for quantification of certain molecule in Active ingredient/FP it can be the active moiety or any other contents
Method type	Reverse phase or Normal phase	Based on the molecule polarity the type of method shall be targeted
Instrument requirement	HPLC, GC, Potentiometer	Based on the availability of chromophores, volatility and other structural and molecular nature of the moiety the method shall be explained.
Sample characteristics	Solid, Liquid, Powder for oral suspension, suppositories, extended release tablets	The sample extraction technique shall be targeted, the necessity of sonicator, mechanical shaker, centrifuge, filters could be defined.
Standard and sample Preparation	Diluent	Justified based on the solubility and pKa of the drug
Method application	Assay of APPI/FP/In process samples	The profiling begins with target of developing common method quantifying API, FP, In-process analysis, Stability samples, Uniformity of dosage unit's analysis.

Critical Quality attributes. A chemical, biological, physical, microbiological properties that must be inside a proper limit or dispersal to ensure the desired product excellence [19]. In case of process related CQA the drug products quality traits such as assay, Dissolution, chromatographic purity, uniformity of dosage units, residual solvents, water content, microbial limits, viscosity in case of creams, suspensions, emulsions and medicament in soft gelatin capsules are considered as critical quality traits. Whereas in case of AQbB considering a HPLC method development as typical example, tailing of peak, Theoretical plate count, resolution between impurities and between impurities and main analyte, peak purity, capacity factor, LOQ and LOD achievement shall be considered as critical quality attributes. In case of dissolution method development, the sink condition requirements based on the solubility of drug, developing a method without cone formation, cross linking of gelatin which retards the release of upon storage of hard gelatin and soft gelatin capsules shall be considered as CQA, In pharma R & D's which work on generic market, the development of dissolution media to compare the dissolution profile with that of the reference listed drugs the profile comparison the mathematical approach such as F1 or similarity factor and F2 or dissimilarity shall be considered as CQA[20].

Identify a CQA based on the extreme of harm to patient safety and efficacy as a result of analytical result falsification. Identify a CQA before considering risk control and don't change because of risk management.

Primary method scouting. With the CQA goals defined, method scouting can begin, classically with the literature survey, physical and chemical properties of the moiety, flowcharts and decision trees to guide the analyst to begin with among the choices. Automation in scouting experiments is ideal procedure. For example, a well-organized and complete experimental plan based on methodical, scouting of three crucial components of a reversed phase HPLC method (column, pH and organic modifier) shall be chosen and finalised [21]. The product of the method scouting will be a basic method which satisfies all the ATPs defined prior for the method.

Risk Assessment. Risk assessment is generally understood that hazard is well-defined as the mixture of the possibility of occurrence of harm and the severity of it [22]. In aid of explaining risk assessment three questions are often helpful.

1. What could go wrong?

2. What is the probability it may go wrong?

3. What are the severities?

Some of the well-recognised risk assessment tools in AQbD are FMEA, Ishikawa cause and effect analysis or Fish bone diagram and prioritization method [23]. FMEA assessment could be performed using a simple spread sheet where the failure type, impact, severity, causes and corrective action with measures could be assessed. An FMEA uses few measures to assess a failure: 1) the severity on analytical result, 2) frequency and 3) Ease of detection. Evaluator must set on a rating between 1 and 10 (1 = low, 10 = high) for the severity, occurrence and detection level for each of the failure modes. After rating the a risk priority number (RPN) could be calculated.

RPN shall be calculated by:

$$RPN = \text{severity} \times \text{occurrence} \times \text{detection}$$

One of the most communal choice to achieve a structured risk assessment is to custom a Ishikawa fishbone diagram or cause-and-effect diagram to recognize possible aspects that may affect the method performance. Fishbone diagrams classes risks in to those related to material, methods, measurements, instrumentation and other factors [24].

Table 4 (a). Typical FMEA for a RP HPLC assay method.

Method	Failure Type	Potential Impact	SEV	Potential Causes	OCC	Detection Mode	DET	RPN
Outline method procedure, step or product being analyzed	Define could go incorrect (based on the Critical method parameter and Critical material attributes assessment)	evaluate the impact on the crucial output variables.	Evaluate the severity to the result? (1 = low, 10 = high)	What reasons the key input to go incorrect?	Frequency of occurrence (1 = low, 10 = high)	Existing control to prevent failure	Ease of Detectability (1 = low, 10 = high)	Risk priority number (SEV x OCC x DET)
Assay method to quantify the content of API in the drug product by RP HPLC method	Placebo peak and analyte peak merged	Resolution between placebo peak and main analyte will reduce	10	pH of buffer (Critical method attribute)	5	pH mentioned in the procedure	2	100
Assay method to quantify the content of API in the drug product by RP HPLC method	Bad peak shape with tailing.	baseline hump at retention time of main peak will be observed	5	Grade of reagent eg., ammonium acetate used for mobile phase	4	Reagent grade mentioned in the procedure	2	40

Table 4 (b). Typical FMEA for a RP HPLC assay method.

Recommended Actions	Responsibility	Target Date	Action Taken	SEV	OCC	DET	RPN
Actions taken or to be taken for decreasing the occurrence of the cause or facilitating the detection?	Person responsible for the recommended action?	Target date executing the recommended action?	Actual actions implemented.	How severe is the effect to the result? (1 = low, 10 = high)	How frequently is this likely to occur? (1 = low, 10 = high)	How easy is it to detect? (1 = low, 10 = high)	Risk priority number (SEV x OCC x DET)
perform DOE considering pH as critical method attribute and create a design space.	Analyst	10 days	pH range clearly defined in procedure	2	2	3	12
perform DOE considering different reagent grades as critical material attribute and create a design space.	Analyst	10 days	set of suitable reagent grades identified and clearly mentioned in the procedure	2	3	4	24

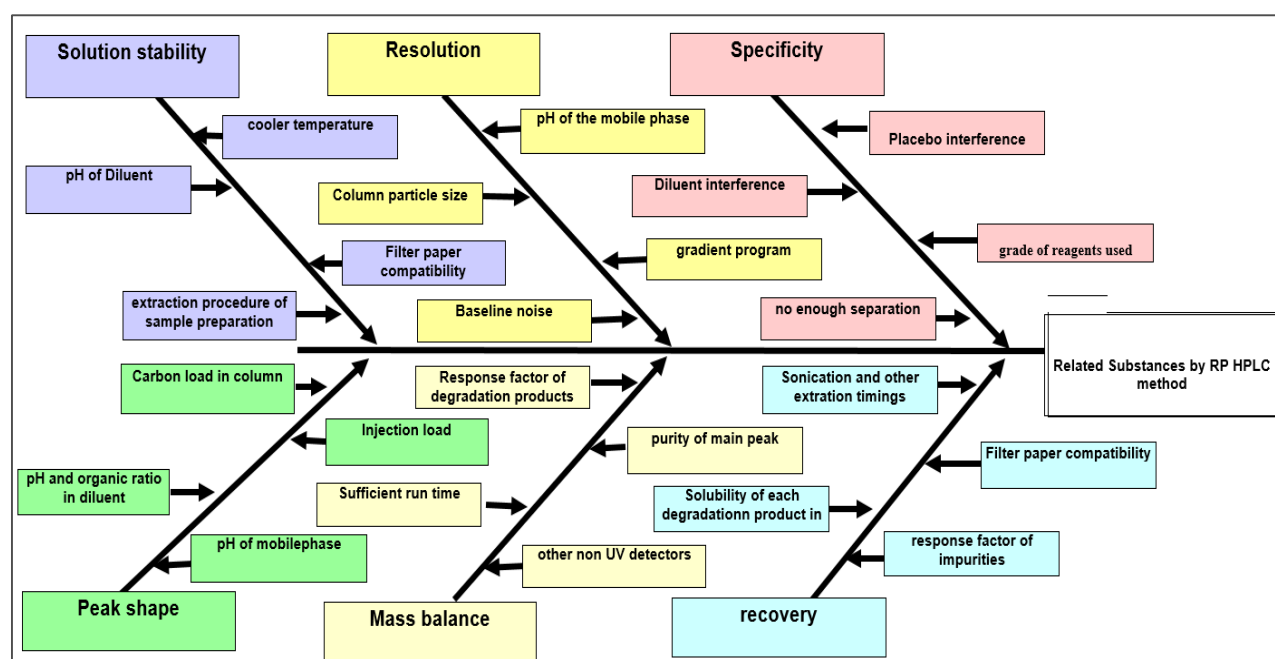


Fig. 2. Ishikawa diagram showing the cause and effect analysis for a Related substances method by RP HPLC method.

Critical material attributes and Critical method attributes. A material or method attribute is critical when a genuine change in that parameter can pointedly influence the quality of the output. Identifying the critical materials such as chromatographic columns, reagents, solvent, material grade and critical method attributes like pH of the mobile phase, column temperature, concentration of organic modifier are part of risk assessment process. Understand and control the variability of the material and method attributes to meet the Analytical target profile by mapping the material and method variables to CQA's.

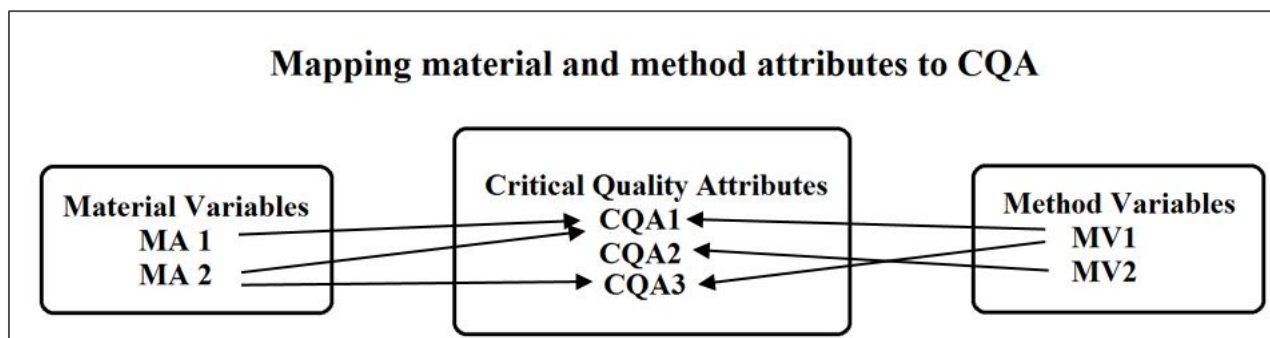


Fig. 3. Understand and control the variability of the material and method attributes to meet the Analytical target profile.

Design of experiments. The tertiary class of risks recognized from the Fishbone Analysis or FMEA or other risk assessment analysis contains instrumental parameters, method variables, material variables those can be itemized and explored with help of Design of Experiments approach (DoE). It can be determined with one variable at time design or multi variables designs and their relations and responses. Multifactorial design provides a chance to screen number of conditions in minimum experiments, then the critical method variables were identified with aid of statistical data and the method operable design space [25]. There are many sorts of DOE design tools and principles stated. Full factorial design for two or three factors study for small studies. A D-optimal type custom DOE design for factors more than 3, when the design space is constrained and the method space contains variables that are not feasible or are impossible to run [26]. Fractional factorial design or Taguchi methods, to achieve reduced variation, prioritizes criticality of variables from high to low [27,28]. Plackett-Burman method (screening few critical factors from large group of variables). Pseudo-Monte Carlo Sampling (pseudorandom sampling) method, use random number generation algorithm [11,29].

Establishment of design space. Method operable design region (MODR) is the multidimensional space establishment based on outcome of the results of DOE upon statistical computation. A change in method within the MODR can provide suitable method performance meeting the ATP. Usually the centre point method of the design space will be finalised and will be validated, further the changes within the established design space is not considered as a change and revalidation with respect to that change is redundant.

Control Strategy. In product AQbD, control strategy is designed to ensure the instant method performance meeting the required ATP. Control strategy is consequent from various data collected during method development phase, statistical data obtained during DoE, MODR, robustness studies, forced degradation studies, stability studies, compatibility studies and method verification process. The capability of the methodology to meet the ATP is well predicted with aid of the above-mentioned data. The control strategy need not be different from the conventional procedure it can be as simple as providing caution notes on the standard testing procedures such as precaution comments like usage of particular grade of reagents, method sensitivity with respect to pH, organic ratio in mobile phase [30].

Continuous Method Monitoring. CMM is the final stage of AQbD. Life cycle management if done by monitoring the method performance over a period to guarantee that the pre-defined ATP is met. Monitoring can be done by using control charts to keep a track on the method performance parameters. This continuous monitoring enables the scientist to proactively identify any out of trend, out of specification results.

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