WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 10, 586-601. Review Article ISSN 2277– 7105

QUALITY BY DESIGN: A NEW APPROCH TO ANALYTICAL METHOD DEVELOPMENT

Ashwini Gayakwad*, Nitin Kanwale*, Kamlesh Mali, Kiran Bhalerao, Sujata Yadav

Department of Quality Assurance Techniques, NDMVP Collage of Pharmacy Nasik, 422002.

Article Received on
10 Aug 2015,

Revised on 30 Aug 2015,
Accepted on 21 Sep 2015

***Correspondence for Author**
Nitin Kanwale
Department of Quality Assurance Techniques, NDMVP Collage of Pharmacy Nasik, 422002.

ABSTRACT

QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include defining a target product quality profile, designing product and manufacturing processes, identifying critical quality attributes, process parameters, and sources of variability and controlling manufacturing processes to produce consistent quality over time. Recent pharmaceutical regulatory documents have stressed the critical importance of applying quality by design (QbD) principles for in-depth process understanding to ensure that product quality is built in by design. This article outlines the application of QbD concepts to the development of analytical separation methods. QbD tools, for example risk assessment and design of experiments, enable enhanced quality to be integrated into the analytical method, enabling earlier understanding and identification of variables affecting method performance.

KEY WORDS: Quality by design, HPLC, Design space, Analytical quality by design.

INTRODUCTION

Quality is heart of pharmaceutical industry .Quality is one of the fundamental criteria in addition to safety and efficacy for any entity to be qualified and approved as drug .for ensuring consistency of performance of pharmaceutical product and system. The recent emphasis has been in building the “Quality” rather than merely testing it. This philosophy form the basis Quality by design (QbD).

The twenty first century began with the pharmaceutical industry using manufacturing technology that have been employed since the 1940s did not make significant change in manufacturing process unless significant compliance or costs saving advantages could justify the high costs and long cycle time needed to gain approval. this often resulted in inefficient, overly expensive process that were ultimately not in the long –term interested not in best long term interests of patient. As a result, the FDA (Food and drug administration) and other agencies around the world have embraced a new paradigm for regulation. The desired state was to shift manufacturing from being empirical, and risk based. juran is often credited with introducing the concept behind Quality by Design (QbD).

The Food and drug administration (FDA), office of Generic drug (OGD) has developed a Question based review (QbR) for its chemistry, manufacturing and control (CMC) evalution of abbreviated New Drug Application (ANDA) QbR is a new Quality attribute. it is a practical implementation of some underlying concept and principles outlined by the FDAs pharmaceutical CGMP for the twenty frist century and Quality by design (QbD) initiatives.

The concept of QbD was mentioned in the ICH Q8 guidance, which states that "quality cannot be tested into products, i.e., quality should be built in by design". 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. This article explores the processes used in developing a market formulation and requisite supportive data, particularly in light of the industry's current movement toward submissions based on quality by design (QbD).

REGULATORY ASPECTS OF QBD

ICH GUIDELINE

QbD ultimately helps to implement Q8 and Q9. Recently, the US Food and Drug Administration introduced quality by design (QbD) as a fundamental pharmaceutical quality model to be considered in the development of pharmaceutical products and processes. QbD principles have also been supported by International Conference on Harmonisation (ICH) guidelines Q8 (R2), Q9, and Q10. ICH Q8 (R2) on pharmaceutical development gives a basis for risk mitigation via the in-depth product and process understanding gained in pharmaceutical development, whereas ICH Q9 on quality risk management develops the principles and some of the tools of quality risk management for assessment, control, communication, and review of the risks of the quality of the medicinal product. ICH Q10 on

pharmaceutical quality systems complements ICH Q8 (R2) and ICH Q9 by establishing a model for a pharmaceutical quality-management system that would facilitate innovation and continuous improvement throughout the lifetime of the product.

QUALITY BY DESIGN (QBD) PRINCIPLE IN METHOD DEVELOPMENT PROCESS

The application of QbD principles to analytical method development is focused on the concept on the of building quality into the method development instead of testing methods for quality after development. A very useful component QbD is the understanding of factor and their interaction effect by a desired set experiments. For the purpose of any analytical method, ruggedness and robustness should be verified early in the method development stage to ensure method performance over the lifetime of the product.

The same QbD principles have been applied to the development of analytical methods, and are termed ―Analytical QbD (AQbD). Analogous to process QbD, the outcome of AQbD is a well understood, fit for purpose, and robust method that consistently delivers the intended performance throughout its lifecycle. The broad knowledge obtained from this process is used to establish a Method Operable Design Region (MODR), a multidimensional space based on the method factors and settings that provide suitable method performance. It is also used to establish meaningful method controls of which system suitability is one component.

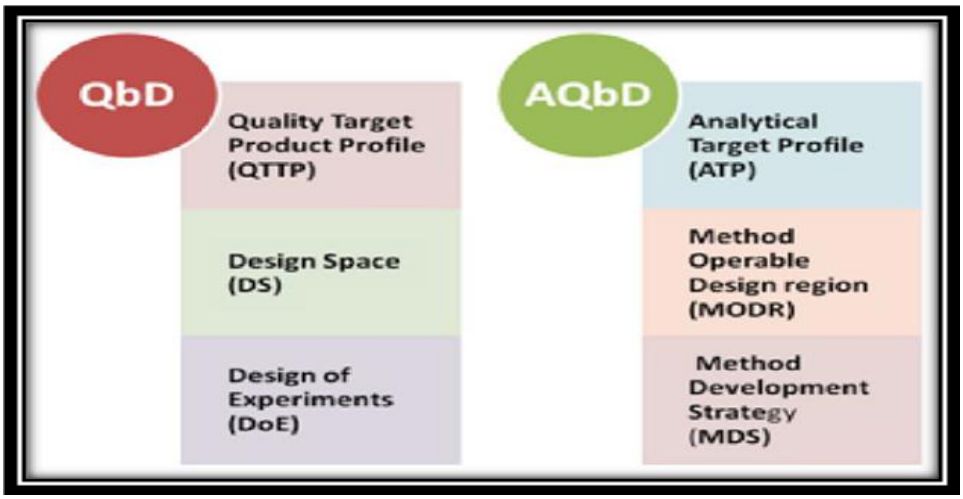


Fig. I: Comparative terminology for QbD and AQbD.

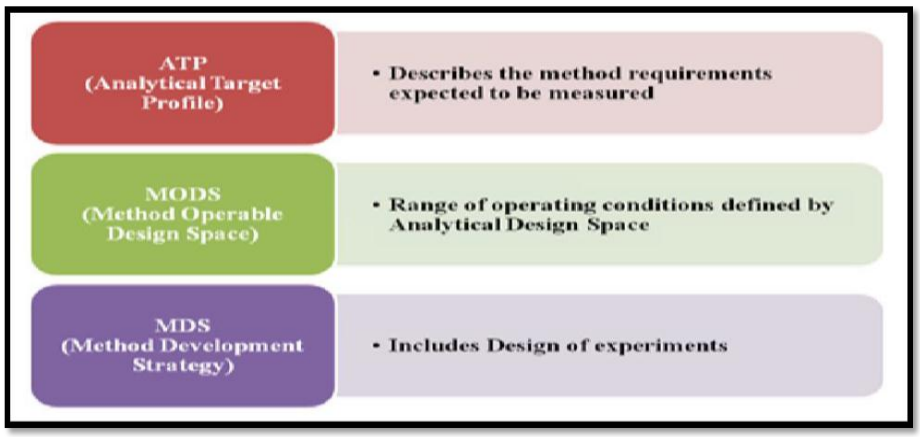


Fig. II: Key definitions for AQbD.

Fig II key Definition for AQbD The first step in designing of analytical methods by using the principle of QbD is the selection of the type of analytical method and the various factors affecting the method. These factors can be classified as primary parameters and secondary parameters. This step involves the study of primary parameters. The parameters are then prioritized based on the extent of the effect caused on analysis. This phase is followed by Screening phase which, calculates approximately the effects of secondary parameters on selected responses (like resolution and selectivity in case of HPLC). Stage which employs the use of computer software as well virtual screening to determine MODS. Analytical testing, is a critical step for pharmaceutical development processes like raw material analysis, in-process checking, release testing, stability studies. To ensure the quality product analytical method should also be in unisonwith the QbD and PAT. Thus, due stress should also be laid on regulatory guidelines for AQbD describing the development of method as per DoE including risk management system and details of quality systems required.

ANALYTICAL TARGET PROFILE

The Analytical target profile (ATP) is a set of criteria that define what will be measured (e.g. the level of specified impurity) and the performance criteria to be achieved by the measurement (accuracy, precision and range), but without specifying the method itself. on the basis of ATP, different analytical method and / or techniques are evaluated in a preliminary investigation to approach the method objective, in general with purpose of achieving maximum selectivity with Adequate efficiency, and improving the reproducibility and repeatability measurements, investigation of method can involve selection of best conditions, for example type of column (size, and composition), pH and organic modifier. After this preliminary experiment, the QbD workflow can start first beginning quality target

product profile (QTPP) and critical quality attribute (CQA). QTPP is define as a "prospective summary of the quality characteristic drug product that ideally will be achieved to ensure the desired quality taking count safety and efficacy of the drug product". Applying this definition to a method means that, first the separation objectives should be well define. Even if the objective can vary, in general the target of the optimization is maximum selectivity with minimum run time, all within known robust working region. For an API this implies separation from the impurities while meeting method performance criteria based on regulatory requirements, for example validation data as defined by the ICH.

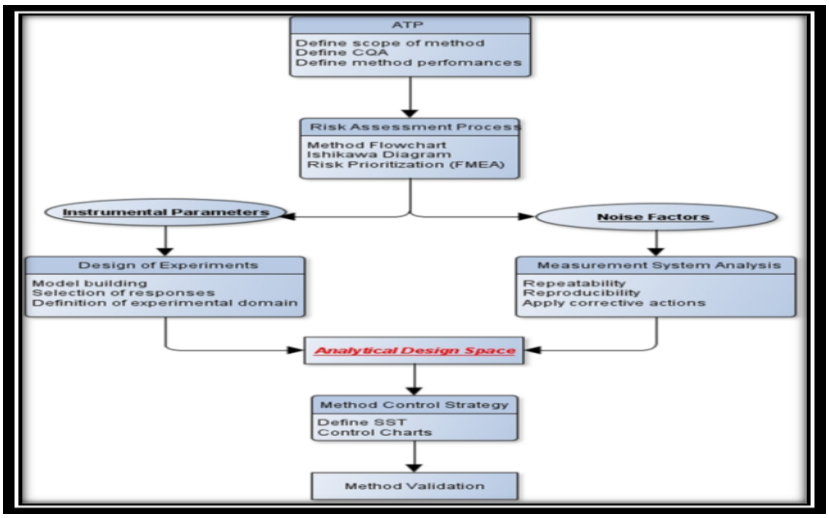


Figure III: Analytical method development in QbD.

"QbD is systematic approach to product and process design and development" hence its begins with determination of goal or method intent. In this emphasis is given on the product and process understanding. ATP is way for method development or it is simple tool for method development. It describes the method requirements which are expected to be measured. In general the goal of the chromatographic method separation, quantification and identification of drug substance, impurity or degradedness. The method requirement will be the accuracy, precision, robustness, ruggedness and so on as described in ICH guideline.

CRITICAL QUALITY ATTRIBUTE (CQA)

CQA is a "physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit range or distribution to ensure the desired product quality" in the analytical methods, CQAs are key response variables, so the chromatogram will be related to mathematical representation of quality. CQA can be divided into two major categories. "Must have" and "intend to have" For instance resolution of a pair of adjacent

peak must be not less than 1.5, and is intended to be not less than 1.8 Some examples of CQAs are the critical resolution RS, run time, efficiency and, in contrast with the QbT approach, robustness. The separation criterion S was recently introduced and was defined as the difference between the retention times measured at the beginning of the second peak and at the end of the first peak of the critical pair. Moreover, even if S and RS are highly correlated, computation of S is easier and its associated uncertainty is lower.

METHOD DESIGN

Method design is prepared for appropriate availability of material and setting various experimental conditions. In this the reagents required are made available. Regional and geographical conditions are taken into consideration. Feasibility of Some example of CQAs are the critical resolution RS, run time, efficiency, and in adjunct instruments is checked and experimental design is prepared. In this use of various flowcharts decision tree can be made for correct implementation. In case of HPLC method development scouting is done. In this large number of experimental conditions were tried (pH, temperature, columns, and buffers). Data are collected and software is generated by entering obtained results in terms of values from actual experiments. Then that data base is generated which helps to predict the effect of various chromatographic conditions in large number. This type of software helps to predict outcome without actual experimentation. Response from design also includes resolution and run time. Hence it is cost effective as well as time effective. Software also assists the future changes in method. Method design also involve selection of different analytical techniques that can be used for particular method development; for example different instrumental method that can be opt like HPLC, LC, Raman and the most effective method amongst is chosen. Among various methods; suitable method to serve the desired purpose is chosen. For example, to determine impurities, HPLC with detector like PDA can be used. In method design, method that meets method requirement is established. Method design may be repeated or modified as and when required throughout the life cycle. Thorough understanding of design intent will form a better Method design.

Method design should be done according to standardized approach. This approach helps in method transfer step from research to quality control department. Method Development Strategy (MDS) includes Design of Experiments (DoE). It is helpful in risk assessment by gaining knowledge about existing method and allows for effective control strategies for critical parameter.

CRITICAL PROCESS PARAMETERS (CPP)

Critical Process Parameters (CPPs) are defined as ―parameters whose variability have an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality, and this statement can be fit perfectly to analytical methods. Parameters are classified into three categories: unclassified, critical or non-critical. The criticality of an unclassified parameter is undetermined or unknown, whereas a parameter is critical when a change in that parameter can cause the product to fail to meet the ATP. Development studies should be able to move unclassified parameters to either non-critical or critical; otherwise they may need to be constrained at fixed values or narrow ranges because they might be critical.

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (Q8) In the framework of method development, DS can be considered as a zone of theoretical robustness as no drastic changes in the levels of the CQAs of the method should be observed. Hence, to define an analytical DS, a widely selected number of factors, also called Critical Process Parameter (CPP)-operating factors (e.g. gradient time) in chromatography that impact on the analytical technique under development has to be studied simultaneously. Usually, the CPPs are obtained from a risk analysis and a prioritization strategy.

RISK ASSESSMENT

According to ICH Q9 Risk assessment can be done in three steps, viz. risk identification, and risk analysis and risk evaluation. Risk identification involves uncovering of all the Potential Method Variable (PMV) and Potential Method Attribute (PMAs) includes all the aspects related to man, material, machine, method, environment and measurement. This can be done with the help of flow chart and check list, etc. Subsequently, Potential Method Variable (PMV) are categorized according to their source of origin. A simplified example of fishbone/ Ishikawa or cause-effect diagram for purity/ impurity LC method is depicted in Figure 1.2. Risk assessment is a valuable science-based process used in quality risk management (that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. (Q8) As per ICH Q9 Risk Assessment is defined as a systematic process of organizing information to support a risk decision to be made within a risk management process (Q9).

There are two risk assessment tools.

- Failure Mode Effects Analysis (FMEA)
- Ishikawa Diagrams (Fishbone diagrams)

A) FAILURE MODE EFFECTS ANALYSIS (FMEA)

In FMEA the variables are ranked on the basis of the likelihood failure will occur (probability), effect on the analytical results (severity), and difficulty of detection (detectability), resulting in a Risk Priority Number (RPN). Factors with an RPN above a cut-off level can then be evaluated by subsequent studies whereas factors with a lower RPN can be eliminated from further study.

Risk Priority Number = Probability × Severity × Detectability.

B) ISHIKAWA DIAGRAMS (FISHBONE DIAGRAMS)

Ishikawa diagrams segregate risks into different categories, for example those associated with instrumentation, materials, methods, measurements, laboratory climate, and human factors. An Ishikawa diagram for an HPLC assay and impurities method was presented, highlighting the different sources of factors, followed by a CNX analysis to decide which factors should be controlled (C)—these were the potential noise (N) factors—and on which experiments (X) should be conducted to determine acceptable ranges. In general, critical conditions in the overwhelming majority of HPLC separations are gradient time, temperature, pH of the aqueous phase, composition of organic modifier, and stationary phase.

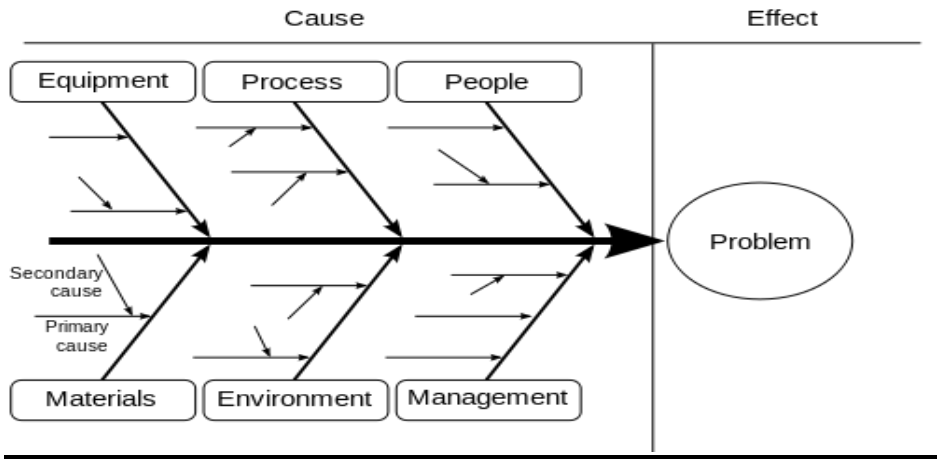
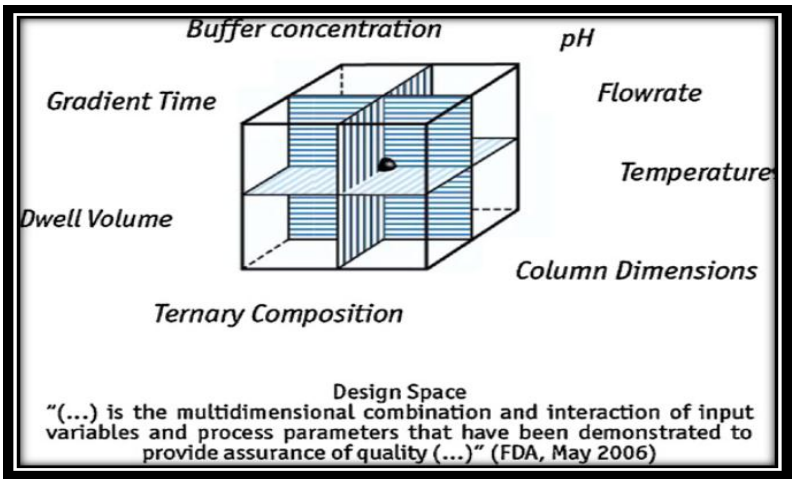


Figure IV: Ishikawa cause-and-effect fish-bone diagram.

DESIGN SPACE (DS)

In ICH pharmaceutical-development guideline Q8, the DS is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Therefore, the multidimensional combination and interaction of input variable corresponds to a subspace, so-called the DS, where assurance of quality has been proved. The DS is necessarily encompassed within the experimental domain, which is the multidimensional space formed by the factor ranges used during method development. The main concept lying behind the ICH Q8 definition of DS is assurance of quality (also known as quality-risk management). This document also states that Working within the design space is not considered as a change. In Figure the working point is in the middle of the cube and represents a result of the best critical resolution. Three different resolution maps are shown here as individual parts of the whole Design Space. The shortcomings of an OFAT approach or of a 2D model are presented in Fig.V where an edge of the cube presents an OFAT method and a plane inside is presenting a 2D model. In Fig. V we can see three planes, each of them corresponding to a 2D resolution map.



In the framework of method development, DS can be considered as a zone of theoretical robustness as no drastic changes in the levels of the CQAs of the method should be observed. Hence, to define an analytical DS, a widely selected number of factors, also called Critical Process Parameter (CPP)-operating factors (e.g., gradient time in chromatography) that impact on the analytical technique under development have to be studied simultaneously. Usually, the CPPs are obtained from a risk analysis and a prioritization strategy. The analytical DS is finally a multivariate domain of input factors ensuring that critically chosen

responses are included within predefined limits with an acceptable level of probability. In order to define the DS of analytical methods; several steps have to be performed. The starting point is to gather and to review all historical information available on the analytical method under development, previously developed methods that are closely related, and the literature and scientific information available on the subject.

METHOD OPERABLE DESIGN REGION (MODR)

MODR of any analytical method also termed as Analytical Design Space (ADS) or Proven Acceptable Range (PAR) is the multidimensional combination and interaction of input variables that have been demonstrated to provide assurance of quality. Once the MODR is established with the help of experimental designs, overlay plotting, and/or numerical techniques of desirability function, it is validated to identify the ―edge of failures. Within the MODR, many a times, it is ideal to identify a region for setting in-house specifications within the firm‘s working environment, also called as Normal Operating Range (NOR) or analytical control space. The fruition of any DoE method depends upon several parameters especially the experimental accuracy and measurement precision. Accordingly, the best practice before validating a MODR would be to perform confirmatory validation runs to ratify the empirical model resulting from a DoE exercise. From the regulatory perspectives, working within MODR should not be considered a change, as a method can be considered robust enough to work within this range.

DESIGN OF EXPERIMENT (DOE)

One can make use of DoE software for AMD too. Traditionally we are used to single variant study. Here DoE help to do multivariate analysis e.g. wavelength, flow rate, sample concentration in HPLC and its impact on retention time, resolution, total run time, column performance etc. Accordingly software can through the best fit equation including design space & near operating range. All factors that can influence the performance of analytical method can be mapped against unit operation within the method. The method design space then continuous by systematically evaluating the impact of each factor. Here the Analyst needs to be trained basic statistics too. Depending upon the complexity, one can use full factorial design. The level can be varied.

Design of Experiments introduced in the 1920s by R.A Fisher is a much more efficient alternative strategy compared to the traditional OFAT approach. DOE has an established mathematical foundation behind the experimental procedures and, therefore, yields the

maximum information for a given amount of data, resulting in experimental resource and time savings. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. Scientists have to use prior knowledge and risk management to identify key input and output variables and process parameters to be investigated by DOE. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those that do not, as well as details such as the existence of interactions and synergies between factors. Based on the acceptable range of CQAs, the design space of CPPs can be determined.

FACTORIAL DESIGN

Factorial designs are used in experiments where the effects of different factors, or conditions, on experimental results are to be elucidated. Factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interactions.

DIFFERENT TERMS OF FACTORIAL DESIGN

Factor

A factor is an assigned variable such as concentration, temperature, lubricating agent, drug treatment, or diet. The choice of factors to be included in an experiment depends on experimental objectives and is predetermined by the experimenter. A factor can be qualitative or quantitative. A quantitative factor has a numerical value assigned to it. For example, the factor concentration may be given the values 1%, 2%, and 3%. Some examples of qualitative factors are treatment, diets, and batches of material, laboratories, analysts, and tablet diluents. Qualitative factors are assigned names rather than numbers.

Levels

The levels of a factor are the values or designations assigned to the factor. Examples of levels are 30 % and 50 % for the factor temperature, 0.1 molar and 0.3 molar for the factor concentration, and drug and placebo for the factor drug treatment.

Effects

The effect of a factor is the change in response caused by varying the level(s) of the factor. The main effect is the effect of a factor averaged over all levels of the other factors. More than two points would be needed to define more clearly the nature of the response as a function of the factor drug concentration. For example, if the response plotted against the levels of a quantitative factor is not linear, the definition of the main effect is less clear. In

many cases, an important objective of a factorial experiment is to characterize the effect of changing levels of a factor or combinations of factors on the response variable.

Interaction

Interaction may be thought of as a lack of additives of factor effects. For example, in a two-factor experiment, if factor A has an effect equal to 5 and factor B has an effect of 10, additivity would be evident if an effect of 15 (5 + 10) were observed when both A and B are at their high levels (in a two-level experiment). If the effect is greater than 15 when both factors are at their high levels, the result is synergistic (in biological notation) with respect to the two factors. If the effect is less than 15 when A and B are at their high levels, an antagonistic effect is said to exist. In statistical terminology, the lack of additivity is known as interaction.

Box Behnken design

Box and Behnken (1960) derived a series of three-level second-order designs that has been very popular, especially for a small number of factors. For t = 3 factors, the Box-Behnken (BB) design requires only 12 runs, plus a recommended $n0$ = 3 center point runs. The comparable central composite design requires 14 runs in addition to the center point replicates. For t = 4, the BB and central composite designs are of equal size, 24 + n0. Box and Behnken (1960) contains only 10 designs, one each for t = 3, 4, 5, 6, 7, 9, 10, 11, 12, and 16. An earlier technical report (Box and Behnken 1958) contains seven additional designs, including a couple of designs for t = 8, although these additional designs have large *redundancy factors*, defined by BB as the ratio of the number of factorial runs to the number of parameters.

CONTROL STRATEGY (CS)

Pharma environment are most dynamic in nature. Newer & stricter standards are emerging. Lot of Pharmacopoeial changes happen quite frequently. So method that is good today may not hold good after some time. Hence the control strategy has to be put in place. This would also address to some extent in risk management. One of the key elements of control strategy would be to have continuous measurement with PAT tools. Fortunately for most of analytical techniques followed today there is generally a facility available to do continuous measurement of method performance.

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and these associated methods and frequency of monitoring and control. (ICH Q10).

As per analytical point of view CS has been defined as the controls on input factors that ensure the method meets both traditional system-suitability criteria and wider performance-related objectives. System suitability tests are a standard part of routine application and are typically established during method validation. A CS generally includes appropriate system-suitability criteria to manage risks, thus QRA can also help to identify a specific control strategy. An appropriate system-suitability test may be the only control element needed to ensure performance of the selected method, because it helps to identify failure modes and can prevent the generation of erroneous results.

CONTINUOUS METHOD PERFORMANCE 9, 13

Gone are the days when method development/ validation department responsibility used to end with successful method transfer. Continuous knowledge transfer within user department and method development/ validation cell is necessary. Plant QC needs to implement Stage III of FDAs PV guidance i.e. Continuous Performance Verification (CPV) from analytical method performance perspective too.

This could involve looking at changing retention time, increasing back pressure/ resolution factor going down gradually/ increasing noise level/ adverse change in number of theoretical plate over repeated column use etc.

Everything may be within limits but there may be an alarm which needs to be highlighted. Entire focus is on studying the variability in method performance and not compliance to the specifications. This is not only applicable to analysis of commercial batches but to stability analysis too. It is highly recommended that for all change controls related to analytical methods, initiated at the plant level, AMV and Validation cell is kept in loop.

CONCLUSION

The paradigm shift from OFAT to QbD (DoE) has supported the pharmacy professionals to cater the needs of combative Quality Assurance. Discerning the importance of analytical

methods in pharmaceutical formulation development, the same principles should be applied to analytical method development also. The main Endeavour of review is to focus on the use of aforementioned Design of Experiment concept in Research and Development and afterwards translation to Quality Assurance Department. The number of research publications reviewed in the paper endorses the fact. The designing increases the confidence in the method developed, as it covers all the aspects and compiles the results categorized under the Design Space. The initial process is costly but ultimately becomes cost effective in case of errors and risks. The benefits of Analytical Quality by Design concept are enormous. The main is during regulatory registration, the changes within the design space for the formulation development do not require refilling. So, to make the process of change in analytical method for registered product unproblematic, regulatory agencies should issue the guidelines pertaining to Analytical Quality by Design. The awareness in the professionals can be ensured by conducting various training programmers, workshops and awareness campaigns. Another important aspect is use of computer software for accurate statistical analysis of data. Cheaper reliable software accessibility will be appreciable. Thus, concluding with the remarks that Analytical Quality by Design is in infancy recently, will grow with regulatory control to its full potential.

REFERENCES

1. Ich Q8 (R2), 2009. Pharmaceutical Development, Part I: Pharmaceutical Development., Http://Www.Ich.Org/Lob/Media//Media4986.Pdf.
2. Ich q9, 2005. Qualityriskmanagement, Http://Www.Ich.Orghttp://Www.Ich.Org/Lob/Media//Media1957.Pdf.
3. Ich Q10, 2008; Pharmaceutical Quality Systems., Http://Www.Ich.Org.
4. Us Food and Drug Administration (Fda), Department of Health And Human Services, Pharmaceutical Quality For The 21st Century A Risk-Based Approach Progress Report, (2013).
5. Us Food and Drug Administration (Fda), Guidance For Industry Pat-A Framework For Innovative Pharmaceutical Manufacturing and Quality Assurance, Fda, Washington, Dc, Usa, (2004).
6. Trivedi B. Quality by Design (Qbd) In Pharmaceuticals. Int J Pharm An Pharm Sci, 2012; 4(1): 17-29.
7. Serena O, Sergio P, Andra F. Application of Quality by Design To The Development of Analytical Separation Methods. Anal Bioanal Chem, 2012.

8. Rozet E, Lebrun P, Debrus B, Boulanger B, Hubert P. Design Spaces for Analytical Methods. Trends in Analytical Chemistry, 2013; 42(1): 157-167.
9. Bhutani H, Kurmi M, Singh S, Beg S, Singh B. Quality by Design (Qbd) In Analytical Sciences: An Overview. Pharma Times, 2014; 46(8): 71-75.
10. Usp Validation and Verification Expert Panel, Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification, Http://Www.Usp.Org/Sites/Default/Files/. (Accessed On June 29, 2014).
11. Steven Weissman. Design of Experiments (Doe) and Process Optimization, A Review of Recent Publications. Org. Process Res. Dev, 2014; 4(2): 1-84.
12. Ayre A, Mane P, Ghude K, Nemade M, Gide P. Implementing Quality by Design-A Methodical Approach In The Rp-Hplc Method Development Process. Int J Adv Pharm Ana, 2014; 4(1): 1-6.
13. Reid L, Morgado J, Barnett K, Harrington B, Wang J, Harwood J, Fortin D. Analytical Quality by Design (Aqbd) In Pharmaceutical Development. Amer Pharm Rev, 2013; 5(4): 1-17.
14. Musters J, Bos L, Kellenbach E. Applying Qbd Principles To Develop A Generic Uhplc Method Which Facilitates Continual Improvement and Innovation Throughout The Product Lifecycle For A Commercial Api. American Chemical Society, Org. Process Res. Dev, 2013; 17(4): 87−96.
15. Sangshetti N, Deshpande M, Zaheer Z, Shinde B, Arote R. Quality by Design Approach: Regulatory Need. Arab J Chem, 2014; 6(4): 1-14.
16. Sumithra M, Ravichandiran V. Review on Quality by Design. Int J Front Sci Tech, 2015; 2(4): 47-56.
17. Zaheer Z, Sangshetti N, Rana A, Hanumant K, Shaikh A. Qbd In Development And Validation Of A Rapid Rp-Hplc For Determination Of Tropsium Chloride In Bulk Drug. J Med Chem Drug Dis, 2015; 5(3): 1-15.
18. Molnar I, Rieger J, Monks E. Aspects of The “Design Space” In High Pressure Liquid Chromatography Method Development. J Chrom Anal, 2010; 12(17): 3193–3200.
19. Bhatt A, Rane I. Qbd Approach To Analytical Rp-Hplc Method Development And Its Validation. Int J Pharm Pharm Sci, 2011; 3(1): 179-187.
20. Schmidt H, Molnár I. Using An Innovative Quality-By-Design Approach For Development of A Stability Indicating Uhplc Method For Ebastine In The Api And Pharmaceutical Formulations. J Pharm Biomed Anal, 2013: 78(79): 65–74.

21. Karmarkar S, Garber R, Genchanok Y, George S, Yang X, Hammond R. Quality By Design (Qbd) Based Development of A Stability Indicating Hplc Method For Drug And Impurities. J Chroma Sci, 2011; 5(4): 49.
22. Jadhav L, Tambe R. Implementation of Qbd Approach To The Analytical Method Development And Validation For The Estimation of Propafenone Hydrochloride In Tablet Dosage Form. Chromatogr Res Int 2013; Available On Http://Dx.Doi.Org/10.1155/2013/676501 23.
23. Box Gep, Behnken Dw. Some New Three Levels Designs For The Study Of Quantitative Variables. Technometrics, 1960; 2(4): 455-75.
24. Sanford, Boltan., Charl, S. Bon., Factorial Design. Pharmaceutical Statistics Practical and Clinical Application. Fourth Edition, 2004; 265-285.
25. Armstrong N, Kenneth C. Factorial Design of Experiments. Pharmaceutical Experimental Design and Interpretation. London, 1996; 131-162.
26. Xavier C, Basavaiah K, Vinay K, Swamy N. Quality By Design Approach For The Development and Validation of Glipizide, An Antidiabetic Drug, by Rp-Uplc With Application To Formulated Forms and Urine. Isrn Chromatography, 2013; 4(4): 1-10.
27. Awotwe O, Agarabi C, Faustino P, Habib M, Lee S, Khan M, Shah R. Application of Quality by Design Elements For The Development and Optimization Of An Analytical Method For Protamine Sulfate. J. Pharm. Biomed. Anal, 2012; 62(2012): 61-67.
28. Monks E, Rieger J, Molnar I. Expanding The Term “Design Space” In High Performance Liquid Chromatography. J. Pharm. Biomed. Anal, 2011; 56(5): 874-879.