Review Article

Pharmaceutical product development: A quality by design approach

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Abstract

The application of quality by design (QbD) in pharmaceutical product development is now a thrust area for the regulatory authorities and the pharmaceutical industry. International Conference on Harmonization and United States Food and Drug Administration (USFDA) emphasized the principles and applications of QbD in pharmaceutical development in their guidance for the industry. QbD attributes are addressed in question-based review, developed by USFDA for chemistry, manufacturing, and controls section of abbreviated new drug applications. QbD principles, when implemented, lead to a successful product development, subsequent prompt regulatory approval, reduce exhaustive validation burden, and significantly reduce post-approval changes. The key elements of QbD viz., target product quality profile, critical quality attributes, risk assessments, design space, control strategy, product lifecycle management, and continual improvement are discussed to understand the performance of dosage forms within design space. Design of experiments, risk assessment tools, and process analytical technology are also discussed for their role in QbD. This review underlines the importance of QbD in inculcating science-based approach in pharmaceutical product development.

Key words: Design of experiments, design space, process analytical technology, risk assessment, Quality by Design, QbD

INTRODUCTION

The annex of International Conference on Harmonisation (ICH), ICH Q8(R2) guidance,[1,2] describes the principles of quality by design (QbD). This guidance further clarifies the key concepts mentioned in the parent guidance ICH Q8.[3] It defines quality as "the suitability of either a drug substance or drug product for its intended use." ICH Q8(R2) defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." The concept and application of the principles of QbD has been an emerging topic in the pharmaceutical industry.[4] In QbD, the product quality is assured by understanding and controlling formulation and manufacturing variables. Thus, the consistent product quality results from the design, control of formulation, and the manufacturing process. This article focuses on the application of QbD for pharmaceutical product development. Application of QbD approach in pharmaceutical product development can lead to robust formulations and high success rate in regulatory approvals. QbD involves the use of multivariate statistics and design of experiments technique.[5]

QbD involves a thorough understanding of the relationship of product performance with product attribute and process.[6,7]

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Traditionally, formulations are manufactured to meet quality control tests outlined in product specifications. If the product is deemed fit for commercial purpose, then it should meet quality control tests. In case of a batch failing to comply with these tests, it is reprocessed or rejected which opens doors for regulatory questions and obvious cost burden. The application of QbD in pharmaceutical product development is systematic, involving multivariate experiments utilizing process analytical technology (PAT) and other tests to identify critical quality attributes (CQAs) based on risk assessments (RAs). The QbD begins with predefined objectives and requires an understanding how formulation and process variables influence product quality.[8] Though end product testing can confirm product quality, it cannot be a part of a process consistency or process control.[9] Figure 1 depicts an overall QbD system where RA and risk control for the product and process are involved.

The important components of product development by QbD are target product profile (TPP), target product quality profile (TPQP), design and development of product, developing the manufacturing process, identifying the CQA, assessment and management of the risks involved in the process, establishment of design space, and defining a control strategy for a product to stay within the design space. Control strategy is the knowledge driven from the relationship between formulation and manufacturing process variables that must be controlled in manufacturing a product of consistent quality. Product lifecycle management further adds to the knowledge base, helps in continuous product monitoring and improvement. Figure 2 shows a schematic representation of how various ICH guidelines dealing with pharmaceutical quality can influence and result in a desired product quality.

KEY ELEMENTS OF QUALITY BY DESIGN

Target product profile

The TPP summarizes the clinical objectives of a dosage form. For a generic product, TPP is determined by the key portions of innovator product labeling. The components of TPP for a generic capsule/tablet dosage forms can be:

Dosage form: Capsules/tablets
Strength: _____.
Route of administration: Oral
Proposed indication: _____.

Target product quality profile

The entire pharmaceutical product development strategy is based upon the TPQP. It is this parameter which determines the design and extent of development. TPQP is the performance-based quality attribute that a product should possess in order to meet TPP. TPQP translates TPP into quantitative tests, for example, assay, impurities, content uniformity, dissolution, bioequivalence, stability, etc. Tests which are vital to the performance of dosage form vis-a-vis meeting therapeutic objectives are included in this section.

Design and development of product

The physico-chemical and pharmacological properties of the active pharmaceutical ingredient (API) determine the critical attributes for pharmaceutical development. The objectives of the product development program using QbD are to achieve desired patient requirements and to identify attributes that drug product should possess to exert intended therapeutic response. The product development must invariably be systematic, scientific, and risk-based to accomplish these predefined objectives. Experience component is an add-on value at various stages to this holistic approach. A strong and thorough understanding of a product and its manufacturing process helps in identifying CQA, which must be controlled to reproducibly produce desired product. Table 1 summarizes the various CQA for drug substance, excipients, in-process materials, and drug product.[10,11] Use of proper statistical methods such as design of experiments, proper RA, and management tools can lead to a successful and knowledge-based product development. Further, knowledge of CQA helps in establishing meaningful and flexible regulatory product specifications. Development knowledge can result in increased manufacturing capability and facilitates QbD.[12]

Pharmaceutical formulations and process can be designed using the following statistical tools.

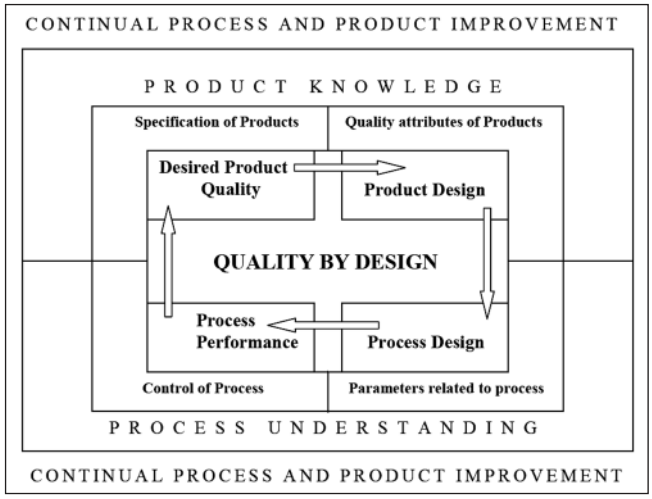

Figure 1: Quality by design system

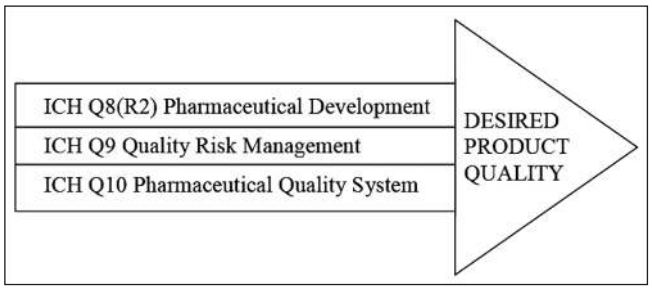

Figure 2: Pharmaceutical quality systems for quality by design

Table 1: Critical quality attributes

Form	Parameter	Critical quality attributes
Drug substance	Physicochemical	Description
		Identification
		Impurities
		pH
		Melting point/range
		Refractive index
		Particle size
		Bulk density
		Polymorphic forms
		Enantiomeric purity
		Water content
	Biological	Activity
		Permeability
	Microbiological	Total count of aerobic organisms
		Total count of yeast and molds
		Absence of specific objectionable bacteria
Excipients	Physicochemical	Concentration
		Stability
		Manufacturability
		Performance of functionality
		Particle size
		Bulk density
		Tap density
		Hygroscopicity
	Biological	Effect on bioavailability of active/s
	Microbiological	Total count of aerobic organisms
		Total count of yeast and molds
		Absence of specific objectionable bacteria
In-process materials		Assay
		Water content
		Hardness and friability of tablet cores (which will be coated)
		pH of a solution
		Disintegration time
		Friability
Drug product	Physicochemical	Description
		Identification
		Assay
		Impurities
		Particle size
		Polymorphic forms
		Tablets (coated and uncoated) and hard capsules
		Dissolution
		Disintegration
		Hardness/friability
		Uniformity of dosage units
		Water content
		Oral liquids
		Uniformity of dosage units
		pH
		Antimicrobial preservative content
		Antioxidant preservative content
		Extractables
		Alcohol content
		Dissolution
		Particle size distribution (oral suspensions)
		Redispersibility (oral suspensions)
		Rheological properties (viscous solutions and suspensions)
		Reconstitution time (dry powder for reconstitution)
		Water content (dry powder for reconstitution)
		Parenteral drug products
		Uniformity of dosage units
		pH
		Particulate matter
		Water content
		Antimicrobial preservative content
		Antioxidant preservative content
		Extractables
		Functionality testing of delivery systems (packaged in prefilled syringes, autoinjector cartridges etc.)
		Osmolarity
		Particle size distribution
		Redispersibility (injectable suspensions)
		Reconstitution time (products for reconstitution)
	Biological	IVIVC (for extended release products)
	Microbiological	Total count of aerobic organisms
		Total count of yeast and molds
		Absence of specific objectionable bacteria
		Parenteral drug products
		Sterility
		Endotoxins/pyrogens

IVIVC: *In vitro - in vivo correlation*

Design of experiments

Though design of experiments is not a substitute for experience, expertise, or intelligence, it is a valuable tool for choosing experiments efficiently and systematically to give reliable and coherent information.[13] Design of experiments is defined as "a structured, organized method for determining the relationship between factors affecting a process and the output of that process."[1] Design of experiments can be used for comparative experiments, screening experiments, response surface modeling, and regression modeling.[14]

Comparative experiments

These are used for choosing a better one between two alternatives. The selection is based on the comparison of average results generated from a sample of data from each alternative. For example, choosing a vendor for API from two or more vendors can be a comparative experiment. Comparative designs with narrow scope are suitable for an initial comparison, whereas with broad scope are suitable for a confirmatory comparison.

Screening experiments

Screening experiments involves the selection of key factors affecting a response. In these, we select relatively small number of factors which have critical effects on the desired response. These are an efficient way to determine the important factors

using minimum number of runs. These experiments can be used as preliminary tools for developing response surface models.

Response surface modeling

This method is used after identifying the critical factors affecting a response. Response surface modeling can be used for hitting a target, maximizing or minimizing a response, reducing variation, making a process robust, and seeking multiple goals.

Hitting a target: This is used to find out the adjustments required to hit a target by fitting a model estimated from a small experiment such as adjustment of a compression machine tool.

Maximizing or minimizing a response: Response surface modeling can be used to increase desired response and decrease undesired responses. Here, we have to carry out experiments with multiple inputs to achieve a better response.

Reducing variation: In some cases, excessive variation in some critical product quality can occur due to some hard to control factors. Then experiments can be carried out with these factors to obtain a flatter surface in the response surface plots which makes the critical product quality more manageable. Second order designs are more useful in these cases. The key attributes of this model can be evaluated by contour and surface plots.

Making a process robust: Using response surface modeling, we can predict the robustness of a process, which yields a critical product quality. Selection of a range for the input factor which yields best robustness for the process can be estimated from the response surface and can be fixed as the operational range for that particular factor such as effect of compression pressure and press speed on tablet dissolution.

Seeking multiple goals: In product development, there will be several desirable product qualities. They may be interrelated and improvement of one can cause worsening of the other such as tablet hardness and disintegration time. These problems can be solved by examining contour plots and response surfaces for these factors.

Regression modeling

These modeling can be used to determine a precise model which estimates the dependence of response variable(s) on process inputs.

Common experimental designs

The selection of the dependent and independent factors should be based on some logic or knowledge gained from the experience. Including all relevant factors is important. Sensible high and low levels should be chosen for the factors and impractical and impossible levels should not be included in the design.

a. Completely randomized designs: Here, the response variable is determined from different levels of a primary factor without taking any other factor into consideration.[15]
b. Randomized block designs: In this case, one primary factor will be there and blocking is used to remove the effect of irrelevant factors that can be controlled.
c. Full factorial designs: In this design, every level of every factor appears with every level of every other factor. There will be high or low levels for the factors. For "n" number of independent factors with two levels, the number of experimental runs required is equal to 2^n.
d. Fractional factorial designs: Here, a carefully chosen fraction of the runs are selected instead of carrying out all the runs in as in a full factorial design. Full factorial designs can quickly become very large as the number of factors increases.
e. Plackett–Burman designs: In cases where only the main effects of the factors are important, these designs are said to be very efficient. They have an experimental run number as a multiple of four. A very large number of factors can be evaluated with a minimum number of runs.
f. Response surface designs: A quadratic or cubic model can give a complete description of process behavior. The curvature in the response surface is caused by the presence of quadratic and possibly cubic terms in the response.[14] Figure 3 shows the representation of how linear, quadratic, and cubic functions of a response changes (from bottom to top of the figure) while the factor level increases (from left to right of the figure). Quadratic models are always sufficient to the pharmaceutical industry. While a two-level factorial design cannot fit a quadratic equation, three-level factorial designs can fit but requires a large number of runs when more than four factors are involved. When a first order model is not adequate and the experiment is close to the optimum response region, a second order model is mostly used to determine the response.[16] For analysis of response surfaces, special designs are used to fit the second order model to the response using a minimum number of runs. The two classical quadratic designs include Box–Wilson central composite designs (CCDs) and Box–Behnken designs.

A CCD is used to build a second order (quadratic) model for the response variable. Linear regression is used in the design to obtain the results. The factor levels are usually coded for the design.[17] They are two-level full factorial or fractional factorial designs. The designs are augmented by a number of center points and other chosen runs. They allow the determination of all the regression parameters that are needed to fit a second order model

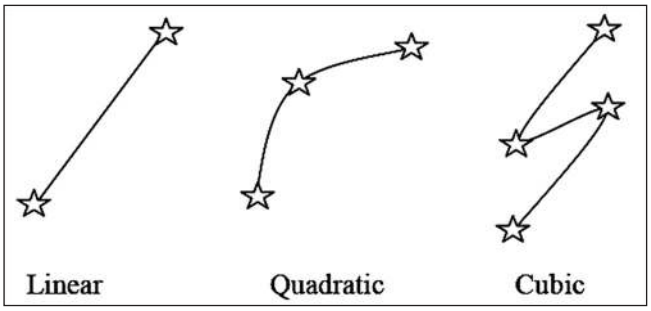

Figure 3: Linear, quadratic, and cubic functions of a response

to a given response. The symbol "α" is used to denote the distance of the axial points (also called star points) from the center point. The number of axial points in a CCD will be twice the number of independent factors. A CCD may be circumscribed (have circular, spherical, or hyperspherical symmetry, and require five levels for each factor), inscribed (a scaled down circumscribed CCD with each factor level of the design divided by α to generate this design; requires five levels of each factor), or face centered (requires three levels of each factor). Rotatability, which gives equal precision of estimation in all directions, is a desired property for any design. A CCD is considered to be rotatable if it gives constant variance of the determined factors corresponding to all new observation points that are at the same distance from the center point.[14,17]

Box–Behnken designs are for three level factors and are widely used in response surface methods to fit second-order models to the response. The design is a combination of two level factorial designs with incomplete block designs. These designs are almost rotatable. Box–Behnken designs are having the advantage that they require only three levels. In addition, it has advantages that there are no runs where all factors are at either the −1 or +1 levels and that there are no runs at the corner points. Corner point runs sometimes are expensive or inconvenient. However, compared to CCD, this design is having limited capability for orthogonal blocking.[14,17]

A contour plot represents a graphical technique for presenting a three-dimensional (3D) surface on a two-dimensional format. It is obtained by plotting constant z slices, called contours, on the two-dimensional format. Contour plot can be used as an alternative for 3D surface plot. The vertical and horizontal axis represents the independent factors, while the lines represent the iso-response values. The response surface and contour plots is explained with figures in the section, describing design space.

g. Three-level full factorial designs: Here, three levels are considered for each factor. The number of experimental runs is given by 3^n where n is the number of independent factors in consideration. Here, the levels are coded as −1, 0, and +1. A third level compared to the two-level designs helps to investigate the quadratic relationship between the response and each of the factors.

Risk assessments

Risk assessments are carried out through proper use of suitable RA tools.

Risk assessment tools

Basic risk management facilitation methods

Flow charts, check sheets, process mapping, cause and effect diagrams, etc., are the most commonly used simple methods for RA and management.[18]

Process mapping is a technique which relates critical process parameters and/or critical material attributes and critical product quality to a response surface derived from an experimental data.[19] For example, development of product specifications to ensure bioequivalence within the limits of acceptable dissolution specifications.

Cause-effect diagram (also called Ishikawa diagram or fishbone diagram) represents all aspects having influence on a critical product quality. The diagram will be having a horizontal line, the end of which points toward the affected product quality. The major influencing factors are then represented as diagonal lines. The influence of the critical process parameters and critical material attributes is then represented as sublines for the diagonal lines.[18,20] Figure 4 shows a basic Ishikawa diagram.

Failure mode effects analysis

This tool can be used to identify any inadequacies in the development of the product. The method systematically identifies, prioritizes, and estimates the risk and prevents failure. The risk involved in changing a process can also be limited using failure mode effects analysis (FMEA). Product and process understanding is a must for FMEA. The risk reduction can be used to manage potential failures, once failure modes are established.[18,21]

Failure mode, effects, and criticality analysis

Here, FMEA is evaluated in terms of its degree of severity of the consequences, their respective chances of occurrence, and their detectability. Thus, criticality analysis is used here to chart the probability of failure modes against the severity of their consequences. Failure mode, effects, and criticality analysis is most used for failures and risks associated with manufacturing processes.[18]

Fault tree analysis

Fault tree analysis (FTA) is a structured, graphical, quantitative assessment tool which makes modeling of complex systems easy. FTA is an excellent tool for evaluating multiple factors affecting product quality. It is useful for both RA and monitoring. In this, method is taken as the root of a logic tree. Only one top event (root) will be there. Each critical process parameters or critical material attributes is added to the tree as a series of logic expressions. Software can be used to calculate failure probabilities from fault trees. FTA mainly is dependent upon the understanding of the experts about the process to identify the causative factor.[18]

Hazard analysis and critical control points

Hazard analysis and critical control points (HACCP) is a systematic, preventive approach for assuring product quality,

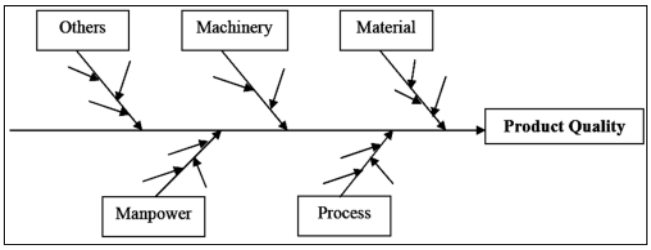

Figure 4: Cause-effect (Ishikawa diagram or fishbone) diagram

reliability, and safety as a means of prevention rather than finished product inspection. HACCP can be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbiological contamination). It is based on technical and scientific principles and is a structured approach against the risk due to the design, development, and production. HACCP is based on the following seven principles or steps:

1. Conducting a hazard analysis.
2. Identifying critical control points.
3. Establishing critical limits for each critical control point.
4. Establishing critical control point monitoring requirements
5. Establishing corrective actions.
6. Establishing record keeping procedures.
7. Establishing procedures for ensuring the HACCP system is working effectively.

HACCP is best utilized when product and process understanding is sufficiently comprehensive. The output of a HACCP analysis facilitates monitoring of critical points in the manufacturing process and other phases of the product life cycle.[18,22]

Hazard operability analysis

Hazard operability analysis (HAZOP) is a widely used method of hazard analysis in the process industries. It assesses risks that are caused by deviations from the design or operating intentions. It uses "guide words" (e.g., no, more, other than, part of, etc.) to relevant parameters and identifies potential deviations. HAZOP can be applied to manufacture process of drug product.[18]

Preliminary hazard analysis

This can be used in the early stages of product development when there is little information on design details or operating procedures.[18] Hazards identified in the preliminary hazard analysis (PHA) are usually further assessed with some other RA tools. PHA consists of:

1. Identification of the possibility of a risk event.
2. Qualitative evaluation of the extent of possible hazard.
3. Relative ranking of the hazard.
4. Identification of possible remedies.

Risk ranking and filtering

It is used for comparing and ranking risks. For each risk, multiple diverse quantitative and qualitative factors are evaluated. Here, a basic risk question is broken into components to identify factors responsible for that risk. Single relative risk score is determined from these factors and the risks are ranked. Weighting factors or cut-offs for risk scores are used for filtering. This is useful to prioritize manufacturing sites for inspection/audit by regulators or industry. Both quantitatively and qualitatively assessed risks can be evaluated using risk ranking.[18]

Quality function deployment

It is a method to transform customer demands into appropriate technical requirements. It may be used to identify and prioritize both critical input parameter and critical product quality.[23]

Supporting statistical tools

These are used for effective data assessment, determining the significance of the data, and decision making. It includes control charts (acceptance control charts, control charts with arithmetic average and warning limits, cumulative sum charts, Shewhart control charts, weighted moving average, etc.), design of experiments, histograms, Pareto charts[21] (pictorial representation used to separate significant factors among many, thus identifying the factors of most concern affecting the desired product quality), process capability analysis, etc. Figure 5 shows a Pareto chart showing standardized effects for factors. The effects or components (even may be more than one of a single factor such as its linear or quadratic or combination effects with other factor) which cross the dotted line is considered to be significant and having a significant effect on the response. In the figure effects, A, B, and C are significant, whereas C and D are not.

Process analytical technology

"Quality cannot be tested into products; it should be built-in or should be by design" is the current approach of FDA[24] to a manufacturing process. FDA defined PAT as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality."[25] The process involves the identification of scientific and engineering principles and variables that affect product quality. PAT is useful in the reduction of cycle times, prevention of reject product and waste, real-time product release, greater use of automation and facilitation of continuous processing. This will generate processes which consistently produce quality products. The understanding of the characteristics of the drug and other components of the drug product is required to design such a process. Undetected variability of raw materials may be manifested in the final product if certain critical attributes of pharmaceutical ingredients are not well-understood or taken into consideration during a manufacturing process. Therefore, a thorough identification and understanding of these attributes should be carried out. However, there are some difficulties that exist for this, such as collecting representative samples from powder samples, which is very much prone to errors. Time defined end points such as blending for a

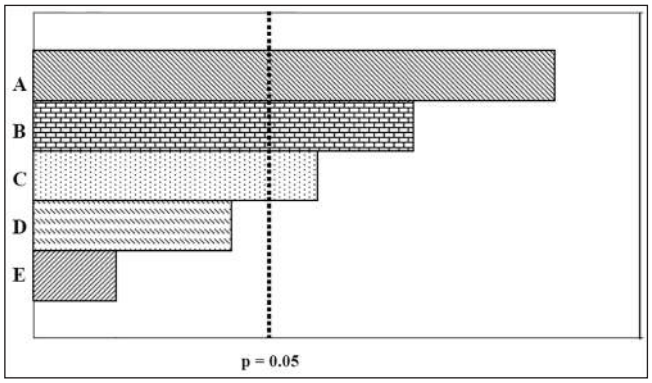

Figure 5: Pareto chart A, B, C, D, and E represents different factors or effects of factors that are evaluated for a particular response

particular time period may not be useful for assuring the product quality as the differences in the critical attributes of the raw materials will not be considered. Formulation design strategies based on the experience of a particular formulator requires testing samples of in-process materials and end products to assess the quality of the resulting products. Tests for each critical attribute are required while current testing is confined to a particular attribute. The former approach can provide valuable information even about the formulation matrix, while in the later, there is every chance to miss these details. New technologies have been identified for nondestructive testing of these critical attributes with minimal or even no sample preparation. This also forms the basis for the PAT. Appropriate use of PAT tools and principles results in identification and thorough understanding of all relevant critical attributes. This will help in process control and optimization. It will also be helpful in overcoming limitation of the time-defined end points and improving efficiency. PAT tools include:

Multivariate tools for design, data acquisition, and analysis
Multivariate mathematical approaches along with knowledge management systems results in scientific understanding of the relevant multifactorial relationships. Design of experiments, response surface methodologies, process simulation, and pattern recognition tools can be used as multivariate mathematical approaches. Statistical evaluation of model predictions can be used to test their applicability and reliability. Appropriate use of these tools results in identification and evaluation of product and process variables.

Process analyzers
Significant advancement have been observed for the process analyzers in recent past and even nondestructive methods are now available for collecting data related to the biological, physical, and chemical attributes of the materials. It involves at-line, on-line, or in-line measurements. Process analyzers are able to provide much data. Real-time control and quality assurance during manufacturing are possible with modern process analyzers.

Process control tools
According to PAT, a process end point is the achievement of desired material attribute rather than a time-defined end point. Process control tools are used to ensure effective control of all product CQA. It also measures the ability and reliability of process analyzers to measure critical attributes.

Continuous improvement and knowledge management tools
Throughout the life cycle of a product, data can be collected, analyzed, and the knowledge can be utilized for the continual product and process improvement.

PAT favors a risk-based approach for a manufacturing process which can facilitate risk-based regulatory decisions and innovation. PAT also supports integrated systems approach and real-time release.

Critical quality attributes

Physical, chemical, or microbiological properties that must be defined in design space to ensure consistent product quality constitute CQA. Critical process parameters may be equipment type, batch size, mixing order, mixing time, other operational conditions, etc. Moreover, critical raw material attributes are its quality and quantity. They should be kept within limits, range, or distribution to ensure the quality. Formulation development begins with thorough understanding of physicochemical and biological properties of API. A process is designed based on these properties, and qualitative and quantitative attributes of raw material are investigated to meet objectives set in TPQP. Process is challenged to evaluate its robustness. Process capability index, which indicates the robustness of process, is derived from six sigma concept. It is the difference of upper and lower limit of specification divided by 6 times standard deviation. Value of more than 1 is indicative of robustness of process.

Direct compression or simple mixing operations are liable to segregation due to the intense vibrations set up in compression or filling machines. Hence, direct CQA for these types of operations will be content uniformity and indirect CQA may be particle size. Particle size uniformity of formulation ingredients can ensure content uniformity. Alternatively, content uniformity can be part of TPQP and particle size can be included in CQA. Validated machine speed ranges can be part of process controls to ensure CQA are complied with.

Similarly, CQA for dry and wet granulation processes are particle size distribution, bulk and tap density, moisture level, etc. Table 1 summarizes the CQAs.

While scaling up a laboratory batch, process parameters are deemed to change. However, if the equipment design is maintained same and scale up is systematically planned, the CQA and design space established at laboratory scale can be extended to commercial size batches. For example, maintaining same percentage occupancy between laboratory scale and commercial scale mixer will ensure reproducibility of blend uniformity achieved with laboratory mixer.

For industries, such as pharmaceuticals and biotechnology, design space is very important.[26] Those process parameters and material attributes are selected for the construction of a design space which when controlled achieve consistent product quality. They can be identified by RA and process development. The RA identifies the product development problems and the risks associated with exposure to these problems. The RA process involves, risk identification, risk analysis, and risk evaluation.

A product is expected to have the defined quality if the operation is carried out within the design space. Thus, it describes an established range of process parameters and/or material attributes that produces product of desired quality. They can be expressed in terms of ranges or as complex mathematical equations. It is advisable to have a design space covering the entire process as it provides enhanced flexibility for the design. However, it is

useful only when the design space has been adequately described by appropriate experimentation.[27] Previous data from the product development stages can also be taken into consideration while constructing a design space. Incorporating QbD into development activities is the prerequisite for the establishment of an operating design space.[28]

Figures 6 and 7 shows design space with the help of contour and response plots, respectively. Similarity factor (f_2) is taken as the response in these plots. The design space is represented by the area inside the curve representing a similarity factor of 50. Outside this curve, similarity factor comes below 50 and the products are not considered to be having similar dissolution profiles. Here, the design space is defined by the area obtained when the combinations of the independent factors A and B gives a similarity factor of 50 or above, that is, inside the curve for 50.

Figure 8 shows an overlay contour plot for two responses, tablet hardness (kg/cm^2), and time for 50% dissolution, t50% (h). In this example, the desired value of hardness is in between 4 and 6 kg/cm^2, whereas that for t50 is between 3 and 4 h. From the figure, it is clear that the shaded portion represents the combinations of independent factors A and B which gives the desired product quality. Thus, the shaded area of the plot represents the design space.

During development and production of dosage formulation, an operational range within design space is identified which consistently leads to the achievement of TPQP, for example, mixing time of 10-20 min (design space) and optimum mixing time at 15 min (control space). Control space is within design space and is narrower than design space. While working within control space, TPQP is assured and will be confirmed by small number of quality control tests. If control space limits are exceeded but are still maintained within design space, quality control tests such as dissolution of drug can provide evidence of achievement of TPQP.

Control strategy

In order to ensure a consistent desired product quality, a control strategy should be designed and managed. A control strategy can include raw material specifications, process controls, in-process testing, and finished product testing. During product development, the influence of process parameters and material attributes on the product quality is to be studied. From this information, the critical process parameters and critical material attributes are identified. These identified critical inputs are then controlled to get the desired product quality. The control strategy adopted should be justified and documented. All the sources of variability should be identified.

A control strategy can be established to control the material and process attributes, for example, to control the unit operations, which have an impact on processing or critical product quality.

PAT can be effectively used for this purpose which will subsequently reduce dependence on design space to monitor quality. In-process tests such as weight variation, disintegration time, and hardness can be used as indicators of process uniformity. Raw materials can be tested for attributes which impact the quality of finished product, for example, particle size, microbial counts, etc.

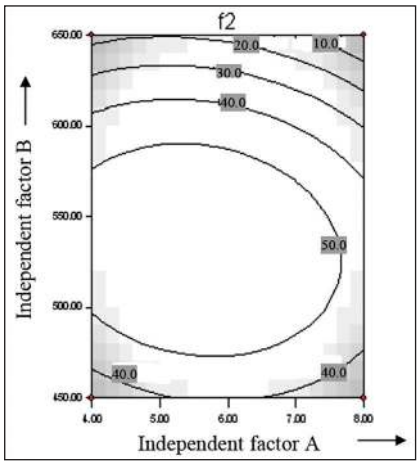

Figure 6: Contour plot for establishing design space

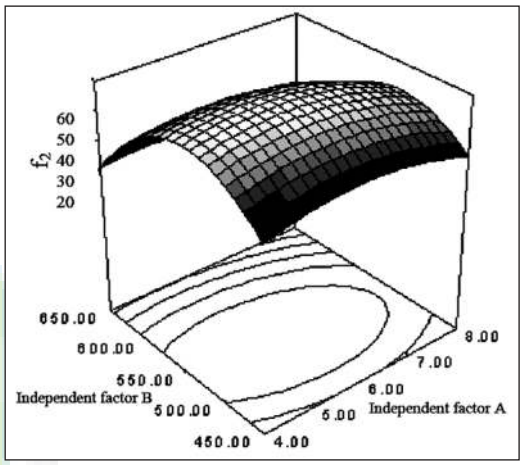

Figure 7: Response surface plot for establishing design space

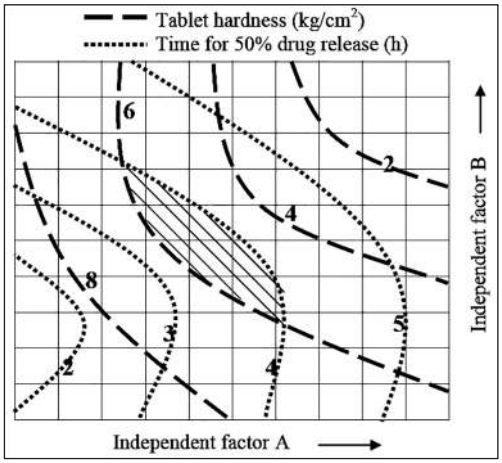

Figure 8: Overlay contour plots showing the design space. The curves shows the iso-response values and their values are indicated on each curve

Product lifecycle management and continual improvement

Efforts have to be made so that a product quality is improved throughout its life cycle. There are four specific pharmaceutical quality system elements to achieve this objective. The outcomes of exploratory and clinical development studies can be considered as useful inputs for product development. The knowledge gained from technology transfer activities provide useful inputs for manufacturing process, control strategy, and process validation which forms the backbone for continued product and process improvement. During commercial manufacturing, the pharmaceutical quality system should identify and evaluate the improvement opportunities. The knowledge resulting from the commercial manufacturing should also be utilized for continual product improvement. In case of product discontinuation, continued product assessment such as complaint handling and stability should be carried out. Retention of the relevant documents and samples of the discontinued products is a regulatory requirement. Opportunities for innovative approaches to improve product quality should always be evaluated depending upon the particular stage of the product life cycle.[29]

Products of desired quality are obtained and the potential areas of continual improvement are identified by the use of a process performance and product quality monitoring system. Timely feedback or feed forward from this system should help in corrective and preventive actions (CAPA). Data management and statistical tools are very useful for executing the control strategy. In CAPA system, the variability of the product or process is identified and actions are taken to prevent it. CAPA should be continued even in case of product discontinuation, overall, this system should result in product and process improvements throughout the life cycle of a product.[29]

Change management system (change control)

A proper change management system should be established in a company which should be able to monitor, approve, and implement changes. The evaluation of the changes is carried out by quality risk management. The impact of all the changes should be evaluated using this system even though a change is within the permissible boundaries of design space. As a consequence, the need for regulatory filings/approval should be considered on a case basis. The approved changes should not be having any deleterious effect on the product quality after its implementation.

Since QbD/PAT management awareness is still low,[30] product quality and process performance should be evaluated properly by the management review board of the company throughout the life cycle of the product. The review should include regulatory aspects, customer satisfaction, process and product performance, and the corrective actions and preventive actions taken. The scope of improvement to manufacture process and product quality should be identified and considered by the management review systems.

CONCLUSION

The concepts of QbD in the new ICH guidance, ICH Q8 (R2), will help industry for a successful product development and expedite regulatory approval. A successful product development strategy requires thorough understanding of QbD principles and the tools for establishing the QbD strategy. Science and risk-based product development strategy are carried out with the help of QbD. Design of experiments, risk assessment tools, and PAT are the major tools for the establishment of QbD principles. Establishment of a design space by QbD provides an opportunity for flexibility in constructing a more meaningful design space. The changes in product and process can be managed better with QbD. Manufacturers can execute certain changes without filing prior approval supplements and can simply notify regulatory authority in annual reports. The economic and resource drain due to exhaustive validation requirements can significantly be minimized. The application of QbD principles can change the chemistry, manufacturing, and control regulatory process into a science and risk-based assessment.

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Conflicts of interest

There are no conflicts of interest.

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