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Reveiw Article

QUALITY BY DESIGN (QBD): A COMPREHENSIVE UNDERSTANDING OF IMPLEMENTATION AND CHALLENGES IN PHARMACEUTICALS DEVELOPMENT

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ABSTRACT

Pharmaceutical industry is constantly looking for ways to ensure and enhance product safety, quality and efficacy. However, drug recalls, manufacturing failure cost, scale up issues and regulatory burden in recent past suggest otherwise. In traditional quality by testing (QbT) approach, the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on implementing quality by design (QbD), a science based approach that improves process understanding by reducing process variation and the enabling process-control strategies. In this regards, pharmaceutical industry is currently undergoing a significant transformation to streamline their R&D process, provide greater manufacturing flexibility and control, and to reduce regulatory burden. However, there is limited understanding and major concerns regarding the implementation of QbD principles in the pharmaceutical arena. The objective of this review article is therefore to provide a comprehensive understanding on various aspects of QbD, along with addressing the concerns related to its implementation.

Keywords: Quality by design, Design of experiment, Pharmaceutical manufacturing, Critical quality attributes, Quality risk management, Design space, Quality target product profile

INTRODUCTION

In past few decades, pharmaceutical companies had spend an enormous amount of resources in their unflagging efforts to assure quality, achieve regulatory compliance, and produce drugs as cost-effectively as possible. Consequently, they employ advance processes and technologies that entail a great deal of scientific sophistication and operational complexity. However, such effort lacks comprehensive, rationale based understanding of these complex processes, associated critical variables and strategies to control these variables, which is pivotal in assuring quality of the product. Little emphasis is paid to identify the root cause of manufacturing failures. Furthermore, no rationale-based approach is followed to predict the effects of scale-up on the final product [1]. This has led to a gap between product quality attributes and their clinical performances, forcing regulatory authorities to set stringent specifications and guidelines for approval of drug products.

In order to overcome these roadblocks, in 2002, US Food and Drug Administration (FDA) had announced a new initiative-Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, intended to modernize the FDAs regulation in regards to pharmaceutical manufacturing and product quality. The initiative challenged industry to look beyond quality by testing (QbT) for ensuring product quality and performance. Additionally, International Conference on Harmonization (ICH) Q8 guideline was published in May 2006 for pharmaceutical product development, and has been complemented by the ICH Q9 on Quality Risk Management and ICH Q10 for a Pharmaceutical Quality System. These guidelines emphasize quality by design (QbD), a science-based approach for designing formulations and manufacturing processes in order to ensure predefined product quality objectives. The fundamental assumption underlying QbD is that the quality of the product can be assured only if critical sources of variability is understood and is suitably mitigated or controlled within a defined design space [2].

In the traditional QbT approach, pharmaceutical quality is defined as the product meeting the pre-specified quality and regulatory specification [3]. QbT framework typically encompasses raw material testing, drug substance or drug product manufacturing process, in-process material testing, and end product testing. The quality of raw materials including drug substance and excipients is monitored by traditional testing methods. If they meet the manufacturer's proposed and/or FDA approved specifications for drug substance or excipients, they can be utilized for the manufacturing of the products. Since only limited numbers of drug product (e.g. tablets) out of several million are tested, drug manufacturers are usually required to conduct comprehensive in-process testing, such as blend uniformity, tablet hardness, tablet disintegration in order to ensure that the outcome of in-process testing meets the FDA approved testing specifications [4]. Furthermore, due to lack of confidence, in the manufacturing processing, on part of FDA, the manufacturers are not permitted to make modifications to the operating parameters specified in the batch record without filing supplements with the FDA [4]. Consequently, pharmaceutical companies incurred high cost associated with manufacturing failures while delaying the approval process due to stringent specification and additional paperwork required by regulatory authorities.

In this regards, with the assertion of regulatory authorities to implement QbD, pharmaceutical industry is undergoing a significant transformation to streamline their R&D process, provide greater manufacturing flexibility and control, and to reduce regulatory burden. However, there is limited understanding and some major concerns regarding the implementation of QbD principles in the pharmaceutical arena. The objective of this review article is therefore to provide a comprehensive understanding on various aspects of QbD, along with addressing the concerns related to its implementation.

Quality by Design (QbD)

Regulatory authorities consider that incremental and unsystematic improvement in unit operations, in isolation, would only have little effect on overall process performance or quality. To assure the quality of the product, a more holistic approach provided by QbD should be adopted. QbD is defined in the ICH Q8 guideline 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" [5]. In manufacturing of new or marketed products, QbD can help in pre-determining the risk potential of various operation, assuring that suitable control strategies can be applied on time. Since Qbd is a science-based approach, it provides a basis for optimizing and improving the manufacturing operation without facing additional regulatory filings or scrutiny. Furthermore, for technology transfer, QbD generated process understanding can make the transition more efficient [6].

Table 1: Quality Target Product Profile (QTPP) for Generic Acetriptan Tablets, 20 mg [9]

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling Tmax in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality Attributes	Physical Attributes Identification Assay Content uniformity Dissolution Degradation Products Residual solvent Water content Microbial Limits	Pharmaceutical equivalent requirement. Must meet the compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and Cmax by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

Table 2: Critical Quality Attributes (CQAs) of Generic Acetriptan Tablets, 20 mg [9]

Quality attributes of the drug product		Target	Is this a CQA?	Justification
Physical attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Un-scored	No	The RLD is an un-scored tablet; therefore, the generic tablet will be un-scored. Score configuration is not critical for the acetriptan tablet.
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for acetriptan	Yes	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of label claim	Yes	Assay variability will affect the safety and efficacy. Process variability will affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content uniformity		Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.
Dissolution		NLT 80% at 30 minutes in 900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.

Components of QbD

A] Quality target product profile (QTPP)

FDA defines QTPP as the quality attributes related to safety and efficacy of the product. It may include route of administration, dosage form, delivery systems, dosage strength(s), container closure system, pharmacokinetic consideration and drug product quality criteria (e.g., sterility, purity, stability, and drug release).

It is important to acknowledge that QTPP should only include patient relevant product performance elements. For example, tablet density or hardness may be included as a specification for process monitoring but may not be included in QTPP. Also, if particle size is

critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size [7].

For an NDA, the QTPP is under development while for the ANDA product, the QTPP is well established based on the properties of the drug substance (DS), characterization of the reference listed drug (RLD) products, RLD label and intended patient population [7, 8]. Therefore, a generic drug product is expected to have same QTPP as that of brand or reference product. A typical example of QTPP for immediate release dosage form for generic product development is described in Table 1 [9].

B] Critical quality attributes (CQA)

Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA is defined as "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" [5]. This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables [3]. For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTTP attributes such as assay, content uniformity, dissolution, and permeation flux will also be a part of CQA as they may be altered by formulation or process variables. List of potential CQAs for immediate release dosage form for generic product development is described in Table 2 [9].

Identification of CQA can be performed based on prior knowledge and/or quality risk management (QRM). Prior knowledge may be attained by literature review, manufacturing experience, technology transfer, stability reports, raw material testing data, adverse event report and recalls. Quality risk management, on the other hand, applies various tools to identify and prioritize potential CQA. QRM is discussed in detail in the next section.

C] Quality risk management (QRM)

FDA defines QRM as a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. The goal of QRM is therefore to identify risks within a process or event, analyzing the significance of these risks, and take appropriate measures to mitigate such risks if deemed unacceptable [10, 11].

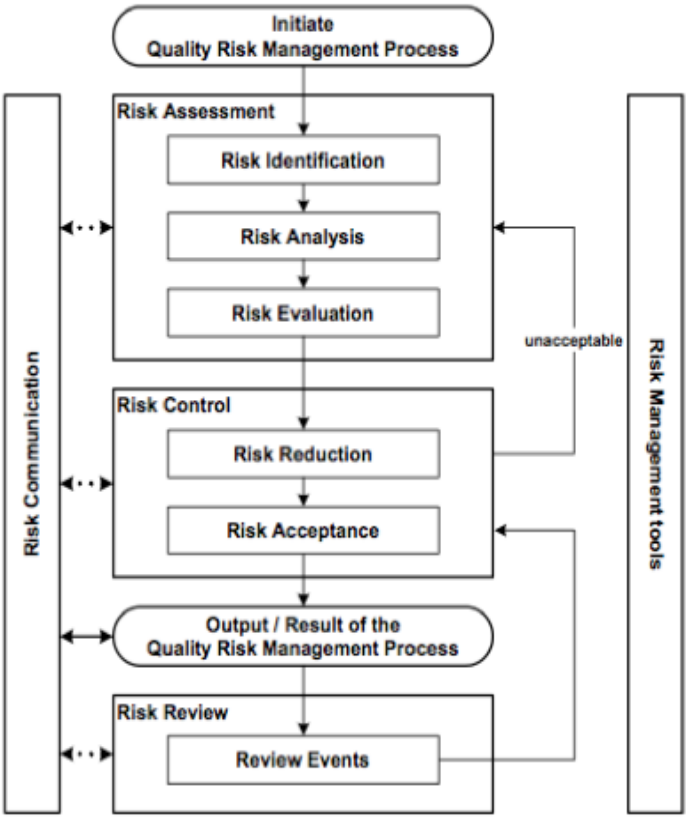

Fig. 1: Overview of typical quality risk assessment process [12]

QRM is integral part of QbD as it helps in identifying the extent of the impact of critical material attributes (CMA) and critical process parameter (CPP) on CQAs, which can eventually assist in prioritizing the CQAs [13, 14]. They are particularly important in complex processes, especially that are involved in cases of biologics or bio-similar.

FDA suggest various tools that can be applied for QRM, among which the relevant ones are discussed below:

Failure mode effects analysis (FMEA)

FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly [15]. Risk control activities can then be performed to avoid such failures modes. Since FMEAs require a good understanding of cause and effects, a thorough process understanding is essential [16].

Case study: QRM of typical manufacturing process by FMEA approach [17]

In this case study, risk identification was performed initially based on the prior understanding in relation to drug substance, excipient and process. Risk analysis and evaluation was then performed based on potential harm(s) associated with each potential risk.

Table 3: QRM of typical manufacturing process by FMEA approach [17]

Risk area	Failure mode	Failure effect	Risk analysis*			
Raw materials			**P**	**S**	**D**	**RPN**
Drug substance	Change in particle size or properties like shape or surface energy	Change in dissolution performance, thus impacting clinical performance	4	5	5	100
Excipient	Increasing binder levels	Slow tablet disintegration affecting clinical performance	4	5	5	100
	Decreasing level of disintegration	Impeded tablet disintegration affecting clinical performance	4	5	5	100
	Magnesium stearate variability affecting wetting of drug particle	Changing dissolution behavior affecting clinical performance	3	5	5	75
	Variability in amount of diluents	Change in granule properties altering disintegration/dissolution	2	5	5	50
Process						
Dry mixing	Insufficient mixing, poor blending	Large range of active ingredient content in the batch	2	3	4	24
Wet granulation	Failure to control granulation end point	Decrease granule porosity, decreased water ingress and decrease dissolution rate	4	5	5	100
	Excessive ware added or holding the wet mass for significant time before drying	Decrease disintegration performance and decrease dissolution rate	3	5	5	75
Dry milling	Incorrect dry milling parameters	Effect on granule size leads to altered dissolution and adverse effect on clinical performance	3	5	5	75
Lubrication	Blending time too long, leading to hydrophobic coat of lubricant around granules	Decreased dissolution rate leads to adverse effect on clinical performance	3	5	5	75

* P is probability, S is severity and RPN is risk product number

The risk score or risk product number (RPN) was determined by following equation:

RPN = probability score × severity score × detectability score

Where, the score was defined prior to the risk analysis stage. A RPN of < 40 was considered a low risk; a RPN of 40–99 was identified as an intermediate risk; and a RPN of ≥ 100 was defined as a high risk. The risk-control strategies were then applied by identifying the unit operations or procedures where the RPN was above a certain threshold (Table 3). After implementing mitigating strategies to reduce the high-risk areas, the RPN values were recalculated to ensure that the projected risks were appropriately minimized.

The risk analysis results were latter document and communicated to the management and experts in QRM assigned to the project. The knowledge gained through this risk assessment was communicated with the employees at the company's other development sites as well as externally through various industry forum presentations. In following the company policy for quality and quality systems, a report describing the rationale, risk-assessment process, action plan, and conclusions were forwarded to internal quality groups for review and future follow-up (e.g., audit, preapproval inspection, risk analysis).

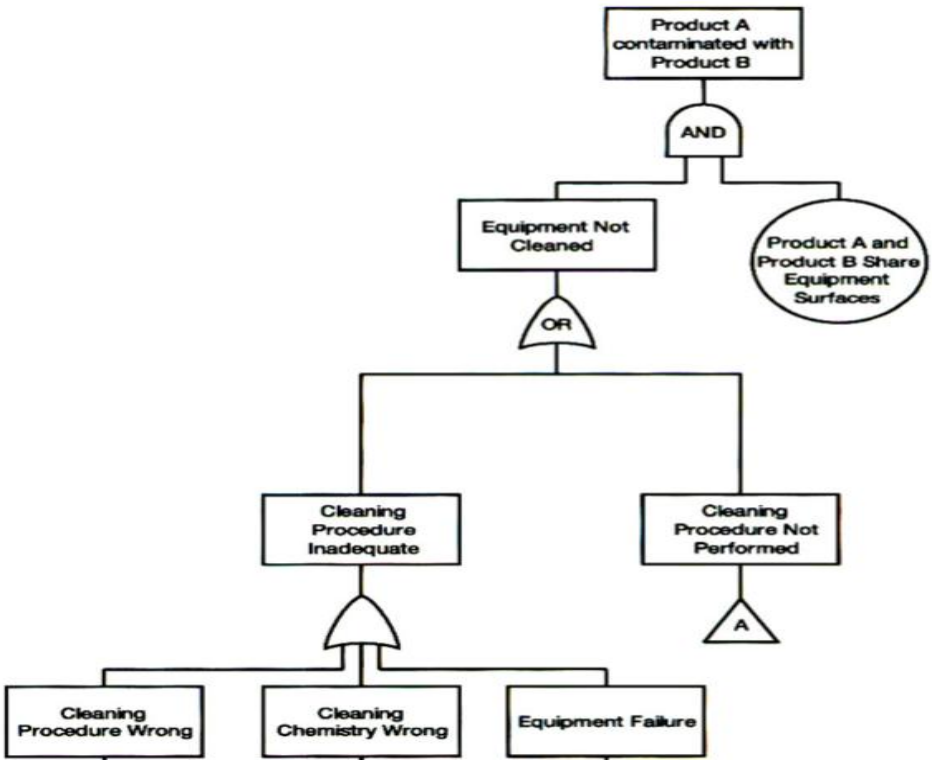

Fig. 2: Fault tree diagram for a cross-contamination between two products [15]

2. Fault tree analysis (FTA)

The fault tree analysis (FTA) was first introduced by Bell Laboratories and is one of the most widely used methods in system reliability, maintainability and safety analysis [16, 18]. FTA is a deductive analysis approach for resolving an undesired event into its causes in a top down fashion [15]. Typically, assumed failures are listed at the top as main event and all of the associated elements in that system that could cause the event are listed as subsequent branches till the root condition or cause is identified [15, 16]. The results are represented pictorially in the form of a tree of fault modes and there relationship are described with logical operators like "AND","OR", etc. [15]. A case study on cross-contamination between two products, is illustrated in form of FTA in Figure 2[15]. As shown in this figure, a fault tree diagram can grow rapidly and can become quite complex.

3. Hazard analysis and critical control points (HACCP)

HACCP provides detailed documentation to show process or product understanding through identifying parameters to control and monitor [16]. The definition of hazard includes both safety and quality concern in a process or product. Examples of hazards within the pharmaceutical setting include environmental aspects of the facility (environmental conditions, hygiene aspects); material flow; manufacturing steps; personnel hygiene and gowning; and technical aspects relating to process design.HACCP consists of the following seven steps: (i) conduct a hazard analysis and identify preventive measures for each step of the process, (ii) determine the critical control points, (iii) establish critical limits, (iv) establish a system to monitor the critical control points, (v) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control, (vi) establish system to verify that the HACCP system is working effectively, (vii) establish a record-keeping system [15]

D] Design space

A design space is a multidimensional combination of input variables (e.g., material attributes), their interactions and process parameters that have been demonstrated to provide assurance of quality [5, 19, 20]. A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. Though according to FDA guideline, defining design space is optional since the product and process understanding can be established without a formal design space, nevertheless, such approach can assist to better understanding and attain overall control of a system.

In this regards, one can apply one-factor-at-time (OFAT) approach, which vary only one factor or variable at a time while keeping others constant. However, design of experiment (DoE) approach that vary several input variables simultaneously are more efficient when studying two or more factors [21, 22]. Factorial designs (full or fractional) and the response surface methodology (RSM) are characteristic tools for this kind of application. The key advantages of using DOE approach are summarized as following [23]:

- Exhaustive information from a minimum number of experiments
- Study effects individually by simultaneously varying all operating parameters
- Can account for variability in experiments, process, materials, or operators
- Able to provide understanding about the interaction between various variables
- Determine acceptable ranges of critical process parameters contributing to identification of a design space

Basic steps involved in DoE approach are as follows:

1. Defining input and output variables and range: Based on prior knowledge and risk assessment the input variables and their range can be defined. Screening design like full or fractional factorial design can also be utilized to identify the range of various variables. The response variable should be a CQA or closely related to them.

2. Select appropriate experiment design and perform the run: The choice of experimental design may depend on the purpose of the study (e.g., a screening, optimization, or robustness study), the factors and interactions involved in the studied and available resources (e.g., literature knowledge, time, labor, cost and materials) [23, 24].

3. Model diagnostic: After obtaining the initial model, foremost step is to check whether the model is appropriate or not. Generally, the significance of a parameter is verified using the analysis of variance (ANOVA) method. ANOVA is a statistical method based on the F-test to estimate the significance of model terms [23]. It involves subdividing the total variation of a data set into variation due to main effects, interaction and residual error. Model terms can be added or eliminated from analysis, depending upon their significance. The new model, with more or fewer model terms, is again forced through this cycle until all terms included in the model satisfy F-test statistics.

Once the overall model satisfies an ANOVA check, the next step is to determine what cannot be modeled (i.e. the errors resulting from the model). This is done using a residual analysis technique. Residuals are the difference between the experimental response and the value predicted by the chosen model. A model is considered a "good fit" if its residuals are normally and independently distributed with zero mean and constant variance. Such distribution can be analyzed either by the normal probability plot of residuals, residuals plotted against predicted values and residuals plotted against experiment run order [23].

4. Illustration of design space: The design space can be tabulated or graphically displayed using various methods. Graphically the design space can be illustration by the following:

A] Contour plots: A contour plot is a graphic representation of the relationships among three numeric variables in two dimensions. Two variables are for X- and Y-axes, and a third variable Z is for contour levels. You can interactively identify, label, color, and move contour levels, and change the resolutions of rectangular grids to get better contouring quality and performance.

B] Three-dimensional plots: These plots are used to illustrate and study the effect of two input variables on an output variable simultaneously. These plots are ideal for showing the process shape, however, contour plots are more useful for determining or displaying acceptable operating ranges for process parameters [22].

C] Overlay plots: When there is more than one quality characteristic in the design space, the use of overlay plots is helpful. The overlay window shows the design space, which indicates the various combinations of the factors that will provide results within the acceptable range.

From FDA perspective, regulatory submission in regards to design space should include the following aspects [25]:

- Description of design space, including critical and other relevant parameters. The design space can be presented as ranges of material inputs and process parameters, graphical representations (contour, interaction or overlay plots) or through more complex mathematical relationships.
- The interaction of various inputs variables (e.g., material attributes and/or process parameters) and their relationship with the CQAs. Interaction plots can be used to illustrates these relationships
- Data supporting justification of design space, which can include but not limited to historic knowledge base, conclusions from QRM and experimental studies.
- The relationship between the proposed design space and other unit operations or process steps.

- Results and conclusions of the studies, if any, of a design space across different scales.
- Justification that the control strategy ensures that the manufacturing process is maintained within the boundaries defined by the design space.

E] Control Strategies

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures 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 the associated methods and frequency of monitoring and control." A control strategy ensures that the process is maintained within the boundaries described by design space.

Specifically, the control strategy may include [26]:

1. Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on process-ability or product quality.
2. Product specifications
3. Procedural controls
4. Facility controls, such as utilities, environmental systems and operating conditions
5. Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
6. A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

It is important to appreciate that when developing a control strategy, a manufacturer can consider implementing single or multiple points of control for a specific CQA, depending on the risk associated with the CQA and the ability of individual controls to detect a potential problem. For example, with sterilized drug substances or biotechnological/biological products, there is an inherent limitation in the ability to detect low levels of bacterial or viral contamination in the drug substance[27]. In these cases, endproduct testing is considered to provide inadequate assurance of quality, so additional points of control (e.g., attribute and in-process controls) are incorporated into the control strategy.

QbD and ANDA

Historically, FDA ensured high quality of generic drug products by requiring two fundamental evidences during ANDA filling- pharmaceutical equivalence and bioequivalence. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration. Bioequivalence, on the other hand, refers that the rate and extent of absorption of the test drug has no significant difference with that of the reference drug, when administered at the same molar dose under similar experimental conditions in either a single dose or multiple doses.

While this approach has been successful, it should be acknowledged that majority of generic drug products approved under this paradigm were solution and immediate release oral products, which are inherently simple in design [28]. Drug products, however, have increased in design complexity to encompass modified (oral) release products, transdermal delivery systems, medical devices and other complex dosage forms. As these drug products have increased in complexity, especially in likes of modified release products, transdermal delivery systems and medical devices, the review paradigm to ensure the quality of generic products must also evolve to provide assurance of high quality in generic drug products [28].

In this regards, from January 2013, FDA has implement QbD into their Abbreviated New Drug Applications (ANDA). Despite the initial resistance from the pharmaceutical companies, in the recent International Forum Process Analytical Chemistry (IFPAC) meeting, Dr. Daniel Peng from FDA reported that there is a steady increase multiple elements of QbD in recent ANDA filings (Table 5).

Table 4: QbD implementation in recent ANDA filings

Month/year	% ANDA including multiple QbD element
June 2012	24.6
July 2012	25.5
August 2012	53.3
October 2012	62.5
January 2013	82.9 (as of 1/13/2013)

However, three key observations were found in the recent QbD based ANDA filling-

1. Exhaustive information being presented with no justification or interpretation of data. Often there were no conclusions from the data presented.
2. Improper use of basic QbD terminology, such as CQA's, CPP's and, in particular, design space.
3. Prior knowledge is often presented without necessary context or justification for its use.

Such issues may indicate an ineffective communication and collaboration between FDA and generic drug companies in regards to QbD implementation. It is expected that as the time will progress, more effective knowledge database will be developed and communicated from both sides that can help in resolving these critical issues.

Advantage of implementing QbD

1. The ability to design products and processes and bring fewer setbacks at critical stages such as scale-up, validation, and transfer.
2. Since the operation is working in a well-defined design space, it allows greater flexibility of adjusting variables within such space.
3. Greater regulatory flexibility based on a science-based approach to risk management.
4. Ability to continue to optimize and improve the manufacturing operation without facing additional regulatory filings or scrutiny.
5. Faster time to market and reduced rework, resulting in reduced costs and increased revenues.

Challenges

1. Lack of understanding regarding the pharmaceutical process is the cause and also the major limitation for Qbd implementation. Pharmaceutical companies are traditionally tuned to care more about the end product, with little emphasis on the science-based understanding of the process involved.
2. Collaboration and consensus between field inspectors and the FDA review and compliance sectors on how to handle QbD remains an unmet challenge.
3. The majority of pharmaceutical companies feels that there is a need for a more tangible guidance on how to actually implement QbD. Companies wanted clarification from FDA on QbD terminologies, acceptable methods, criteria to select and deselect critical quality attributes, standards by which to judge adequacy of controls, and criteria for analytical method substitution.
4. There is a need for greater cooperation across multiple disciplines within the company, including process development, manufacturing, and quality control for effective implementation of QbD.
5. Pharmaceutical companies also feels that QbD would slow time to file approval application, or could provide unnecessary information to the regulatory authority that might create an obstacle in the approval process.

CONCLUSION

QbD is an essential tool that fosters process understanding that is pivotal in assuring product quality and performance. It

encompasses various functions such as technology transfer, control checks, deviation reduction and analytical methods development and improvement. Furthermore, since the quality it integrated in each process operation, regulatory authorities are more comfortable in approving the drug application. However, for pharmaceutical companies, the key issue is to understand the scientific principle of QbD and its implementation methodology. The regulatory authorities also need to harmonize the regulatory requirement and understanding across their departments. It is accepted that the challenges and concerns associated with the implementation of QbD can only be resolved if there is efficient communication between the industry and the regulatory bodies.

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