

Quality by Design (QbD) : A new concept for development of quality pharmaceuticals

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ABSTRACT

Quality by Design (QbD) has become a new concept for development of quality pharmaceutical products, It is an essential part of the modern approach to pharmaceutical quality, QbD is a best solution to build a quality in all pharmaceutical products but it is also a major challenge to the Pharmaceutical industry whose processes are fixed in time, despite inherent process and material variability, Under this concept of QbD throughout designing and development of a product, it is essential to define desire product performance profile [Target product Profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA). On the basis of this we can design the product formulation and process to meet the product attributes. This leads to recognise the impact of raw materials [critical material attributes (CMA)], critical process parameters (CPP) on the CQAs and identification and control sources of variability. QbD is an emerging idea which offers pharmaceutical manufacturer with increased self-regulated flexibility while maintaining tight quality standards and real time release of the drug product, This paper discusses the pharmaceutical QbD and describes how it can be used to develop the pharmaceutical products well within the specified period of time.

Key words: Quality by Design (QbD) Target Product Profile (TPP), Target Product Quality Profile (TPQP), Critical Quality Attributes (CQA), Critical Material Attributes (CMA), Critical Process Parameter (CPP)

INTRODUCTION

The concept of QbD was mentioned in the ICH Q8 guideline, which states that "quality cannot be tested into products, i.e., quality should be built in by design" According to ICH Q8 QbD is defined 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 [7]. QbD encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. In 2002, the FDA announced a new initiative (cGMP for the 21st Century: A Risk based Approach) [1]. This initiative intended to modernize the FDA's regulation of pharmaceutical quality, and establish a new regulatory framework focused on QbD risk management, and quality system. The initiative challenged industry to look beyond quality by testing (QbT) for ensuring product quality and performance. An important part of QbD is to understand how process and formulation parameters affect the product characteristics and subsequent optimization of these parameters should be identified in order to monitor these parameters online in the production process.

This paper discusses the pharmaceutical quality by design and describes how it can be used to ensure pharmaceutical quality with emphasis on solid oral dosage forms of small molecules. The pharmaceutical industry works hard to develop, manufacture, and bring to market new drugs and to comply with

regulatory requirements to demonstrate that the drugs are safe and effective. 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). It outlines activities that should be performed early in the drug development process before initiating manufacturing and attempting market entry.

The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question based review (QbR) for its chemistry, manufacturing and controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs). QbR is a new quality attributes. It is a concrete and practical implementation of some underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the twenty-first century and quality by design (QbD) initiatives [12].

Pharmaceutical Quality by Testing: In this system, product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing.

The quality of raw material including drug substance and excipients is monitored by testing. If they meet the manufacture's proposed and FDA approved specifications or other standards such as USP for drug

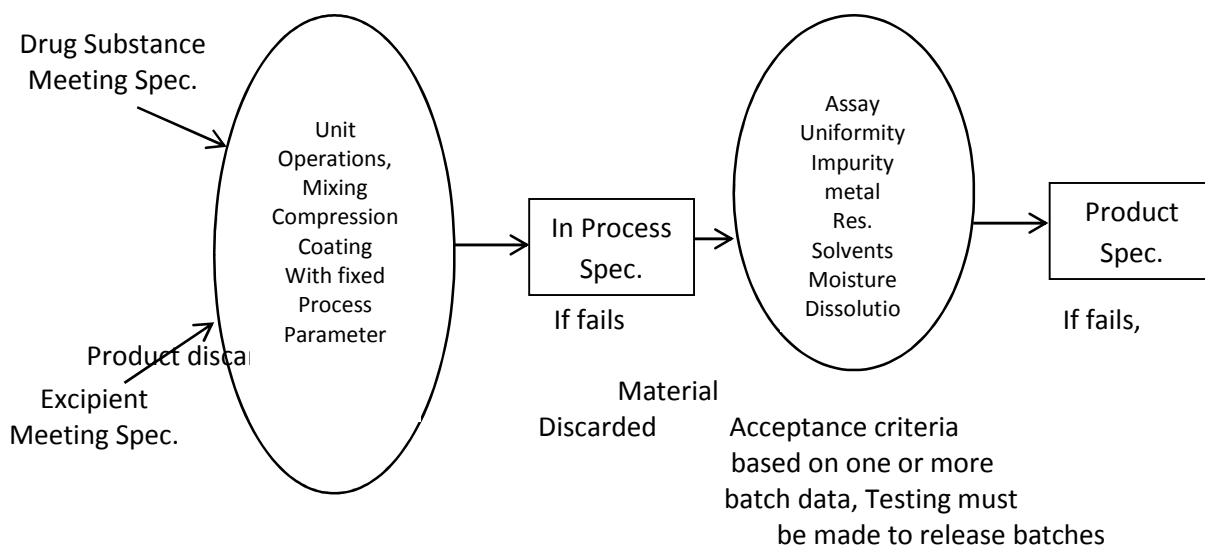


Fig. 1: Quality control diagram using QbT.

substance or excipients, they can be used for manufacturing of the products. Because of uncertainty as to whether the drug substance specification alone is sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. A change to the drug substance manufacturing process may require the drug product manufacturer to file supplements with the FDA.

Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specification. If not, they are discarded. Root causes for failure are usually not well understood. The manufacturers risk ongoing losses of the product until the root causes of failure are understood and addressed or FDA approves supplements to revise the acceptance criteria to pass the previously failed batches. Figure 1 shows a simplified quality control diagram under the current quality by testing (QbT) [2].

Pharmaceutical Quality by Design: ICH Q8 defines quality as the suitability, of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity. Pharmaceutical QbD is a systematic, scientific, risk based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and processes understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives [9]. QbD identifies characteristic that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with desired characteristics. In order to do this the relationship

between formulation and manufacturing process variables (including drug substance and excipients attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time. Figure 2 shows a simplified quality control diagram under the current Quality by Design (QbD).

Enablers of Quality by Design: Knowledge management and quality risk management are two of the primary enablers of QbD. They play a critical role both in development and in the implementation of QbD. They are instrumental in achieving product realization, establishing and maintaining a state of control, and lastly facilitating continual improvement. A brief description of the two enablers and their utility is provided in the following sections [14].

Quality Risk Management: Quality risk management (QRM) is a key enabler for the development and application of QbD. During development, it enables resources to be focused on the perceived critical areas that affect product and process. It is one of the tools that provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It also facilitates continual improvement in the product and process performance throughout the product life cycle.

Knowledge Management: Product and process knowledge management is an essential component of quality by design and must be managed from development through the commercial life of the product, including discontinuation. It is a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, processes, and components. This also emphasizes on a

transparency of information from development to commercial and vice versa. Prior knowledge comprises previous experience and understanding of what has been successful or unsuccessful, and recognition of issues, problems, or risks that may occur and need to be addressed.

Examples of prior knowledge include the following:

- Knowledge gained about the drug substance and/or drug product from early development work
- Knowledge of the properties of materials and components used in other products and the variability of associated physicochemical and functional properties
- Knowledge from related products, manufacturing processes, test methods, equipment, systems, and so on
- Knowledge from previous product and process development projects, both successful and unsuccessful
- Knowledge from the published scientific literature
- Experience from the manufacture and testing of related dosage forms and products, including deviations, customer complaints, etc.

Prior knowledge, be it from the literature, experience with prior compounds/processes that are similar provides the basis for the initial risk assessments and influences a number of decisions that are made. Therefore, a good understanding of the documentation relating to prior knowledge referenced in risk assessments and DoEs is a must for the success of QbD.

Elements of Quality by Design: ICH Q8: Pharmaceutical Development discusses the various elements of quality by design. These in combination with the enablers form the fundamental basis for the QbD approach to development. Figure 3 provides a pictorial representation of the typical elements of QbD. This section describes the various elements in

detail and provides examples of the elements for controlled release (CR) products.

Certain Key Aspects of QBD Include

The Target Product Quality Profile (TPQP): Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development — “planning with the end in mind.” More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve. The target profile is a summary of the drug development program described in the context of prescribing information goals [4,5]. The TPP can play a central role in the entire drug discovery and development process such as: effective optimization of a drug candidate, decision-making within an organization, design of clinical research strategies, and constructive communication with regulatory authorities. TPP is currently primarily expressed in clinical terms such as clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, over dosage, etc. Thus, it is organized according to key sections in the product’s label. TPP therefore links drug development activities to specific statements intended for inclusion in the drug’s label. Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. TPQP is related to identity, assay, dosage form, purity and stability

- Tablet Characteristics
- Identity
- Assay and Uniformity

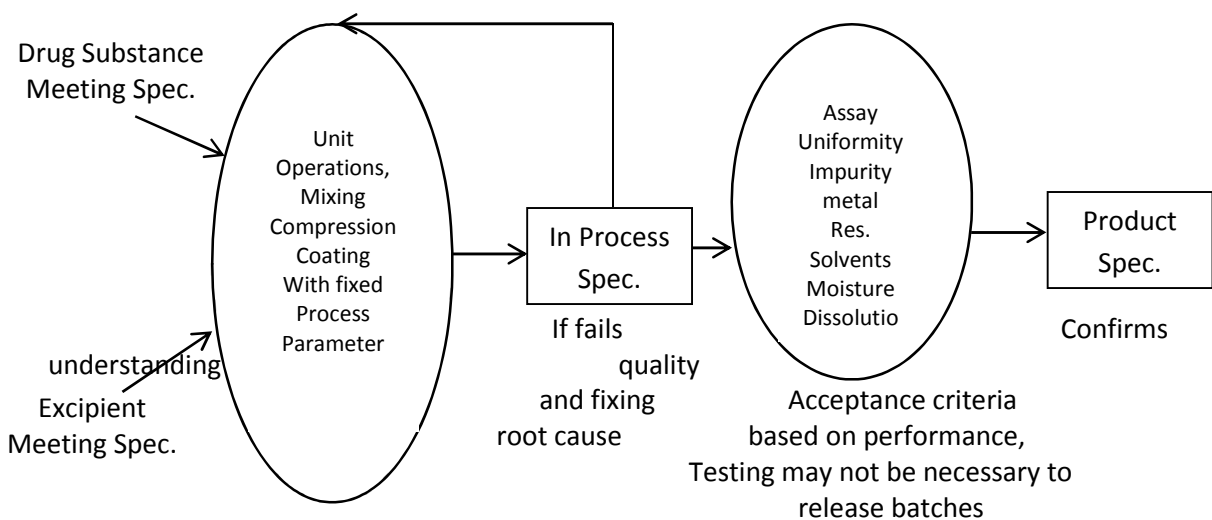


Fig. 2: Quality control diagram using QbD.

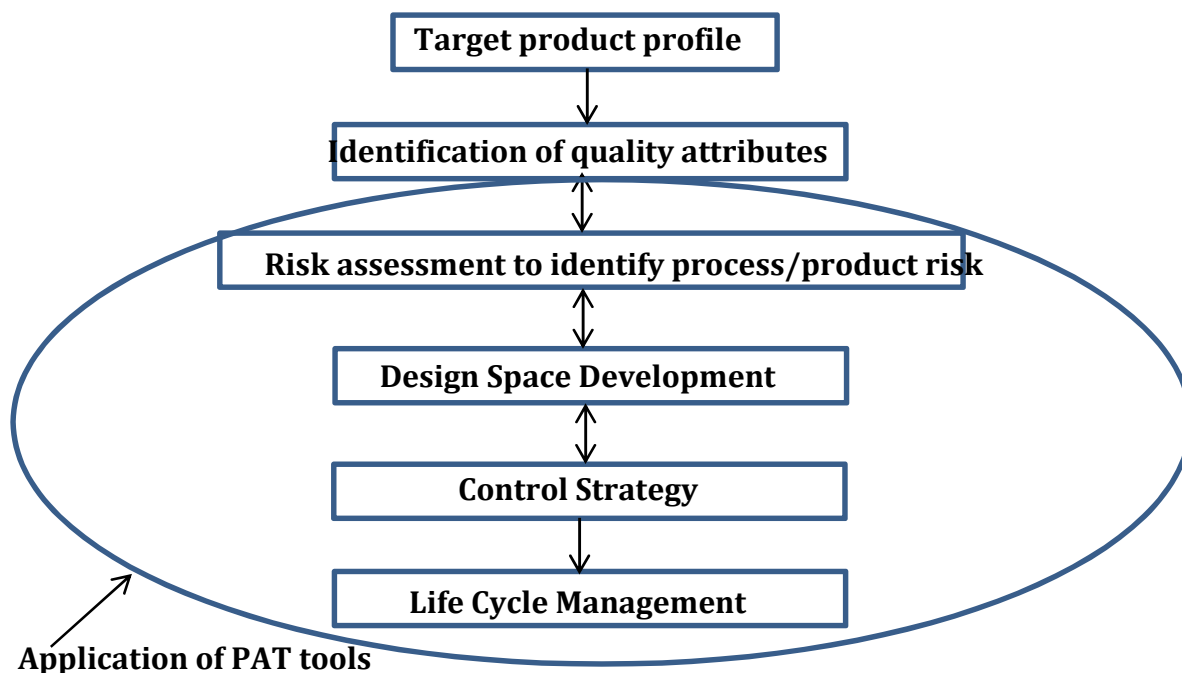


Figure 3: Elements of quality by design

- Purity/Impurity
- Stability, and
- Dissolution

The TPQP of a generic drug can be readily determined from the reference listed drugs (RLD). Along with other available information from the scientific literature and possibly the pharmacopeia, the TPQP can be used to define product specifications to some extent even before the product is developed. Predefined, high quality product specifications make the product and process design and development more objective and efficient. FDA published a recent guidance defining a Target Product Profile (TPP): “The TPP provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. Usually, the TPP is organized according to the key sections in the drug labeling and links drug development activities to specific concepts intended for inclusion in the drug labeling.” When ICH Q8 says that pharmaceutical development should include “identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration”, the consideration of the intended usage and route of administration would be through the TPP.

Identifying CQAs: Once TPP has been identified, the next step is to identify the relevant CQAs. A CQA has been 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” [7]. Identification of CQAs is done through risk assessment as per the

ICH guidance Q9. Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments. Such knowledge may also include relevant data from similar molecules and data from literature references. Taken together, this information provides a rationale for relating the CQA to product safety and efficacy. The outcome of the risk assessment would be a list of CQAs ranked in order of importance. Use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm.

Design Product and Defining Product Design Space: After CQAs for a product have been identified, the next step is to define the product design and design space (that is, specifications for in-process, drug substance and drug product attributes). These specifications are established based on several sources of information that link the attributes to the safety and efficacy of the product, including, but not limited to, the Published literature on other similar products, Process capability with respect to the variability observed in the manufactured lots, Design space, Clinical and nonclinical studies with similar platform products. The difference between the actual experience in the clinic and the specifications set for the product would depend on our level of understanding of the impact that the CQA under consideration can have on the safety and efficacy of the product. In QbD, an improved understanding of the linkages between the CQA and safety and efficacy of the product is required. QbD has brought a realization of the importance of the analytical, nonclinical and

Table 1: Difference between current approach and Qbd approach [13]

Current Approach	Qbd Approach
Quality is assured by testing and inspection.	Quality is built into product & process by design and based on scientific understanding.
It includes only data intensive submission which includes disjointed information without “big picture”.	It includes Knowledge rich submission which shows product knowledge & process understanding.
Here, any specifications are based on batch history.	Here, any specifications based on product performance requirements.
Here there is “Frozen process,” which always discourages changes.	Here there is Flexible process within design space which allows continuous improvement.
It focuses on reproducibility which often avoids or ignores variation.	It focuses on robustness which understands and control variation.
<p>animal studies in establishing these linkages and has led to the creation of novel approaches. In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance [8]. These biopharmaceutical properties include physical, chemical, and biological properties. Biopharmaceutical assessment provides the information needed to select a solid dosage form, to evaluate the developability of a drug candidate, and to determine its classification according to the Biopharmaceutical Classification System (BCS) which is a scientific framework for classifying a drug substance based on its aqueous solubility, dose and intestinal permeability [12].</p> <p>Process Design and Defining Process Design Space: Process and product design and development cannot be separated since formulation cannot become a product without a process. Process design is the initial stage of process development where an outline of commercial manufacturing processes is identified including the intended scale of manufacturing. This should include all the factors that need to be considered for the design of the process, including facility, equipment, and material transfer and manufacturing variables [16].</p> <p>Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time. To demonstrate the reproducibility and consistency of a process, process capability should be studied. Process capability is a statistical measure of the inherent process variability for a given characteristics. The most widely accepted formula for process capability is six sigma [17,18].</p> <p>Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows:</p> $\text{Process Capability Index (CpK)} = \frac{\text{Upper limit of specification} - \text{Lower limit of specification}}{6 \text{ Standard Deviation}}$	<p>If the CpK is significantly greater than one, the process is defined capable. If the process capability is low, Rath and Strong recommend an iterative five step procedure to progressively reduce the variability of the process [18]. These five steps are:</p> <ol style="list-style-type: none"> I. Define: The intended improvement should be clearly stated II. Measure: The critical product performance attributes should be measured to see if they are out of specification and used to the sigma level of the process. III. Analyze: When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability. IV. Improve: The process should be redesigned and/or process controls should be incorporated to eliminate or attenuate the significant root causes of variance. V. Control: The improved manufacturing process should be evaluated and maintained. <p>Design of Experiment (DOE) is structured and organized method to determine the relationship among factors that influence outputs of a process. The overall approach toward process characterization involves three key steps. First, risk analysis is performed to identify parameters for process characterization. Second, studies are designed using design of experiments (DOE), such that the data are amenable for use in understanding and defining the design space. And third, the studies are executed and the results analyzed to determine the importance of the parameters as well as their role in establishing design space. Failure mode and effects analysis (FMEA) is commonly used to assess the potential degree of risk for every operating parameter in a systematic manner and to prioritize the activities, such as experiments, necessary to understand the impact of these parameters on overall process performance. A team consisting of representatives from process development, manufacturing and other relevant disciplines performs an assessment to determine severity, occurrence and detection. The severity score measures the seriousness of a particular failure and is based on an estimate of the severity of the potential failure effect at a local or process level and the potential failure effect at end product use or patient level. Occurrence and detection scores are based on an excursion (manufacturing deviation) outside the operating range that results in</p>

the identified failure. Although the occurrence score measures how frequently the failure might occur, the detection score indicates the probability of timely detection and correction of the excursion or the probability of detection before end product use. All three scores are multiplied to provide a risk priority number (RPN) and the RPN scores are then ranked to identify the parameters with a high enough risk to merit process characterization.

Although FMEA and DOE are not new concepts for the development of manufacturing processes, linking the establishment of design space to the relevant CQA is novel. For example, a granulation step that has a direct impact on several CQAs and a direct bearing on whether the final drug product meets specifications would be expected to undergo a more thorough process characterization and examination of a larger process design space. In contrast, a non-functional coating step that is robust and has no direct influence on any CQA may require relatively limited process characterization.

Defining Control Strategy: Control strategy is defined as “a planned set of controls, derived from current product and process understanding that assures process performance and product quality”. The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements: procedural controls, inprocess controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach [7].

A control strategy may include input material controls, process controls and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production. Every process has a control strategy right now. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness. Manufacturer are also not permitted to make changes to the operating parameters (a large number of UPPs) specified in the batch record or other process changes without filling supplements with the FDA.

This combination of fixed (and thus inflexible) manufacturing steps and extensive testing is what ensures quality under the current system. A combination of limited characterization of variability (only three pilot lots for innovator products and one pilot lot for generic products), a failure of manufactures to classify process parameters as critical or noncritical, and cautiousness on the part of regulator leads to conservative specifications. Significant industry and FDA resources are being spent debating issues related to acceptable variability, need for

additional testing controls, and establishment of specification acceptance criteria. The rigidity of the current system is required because manufacturers may not understand how drug substance, excipients, and manufacturing process parameters affect the quality of their product or they do not share this information with FDA chemistry, manufacturing and controls (CMC) reviewers.

CONCLUSION

The Office of Generic Drugs (OGD) has made decisive moves to integrate QbD concepts into its ANDA drug filing structure by implementing a Question Based Review (QBR) structure. If the rate of QbD adoption is going to increase in the marketplace, the emphasis behind QbD must evolve to a business proposition: one that resonates with the generics industry as a foundation for business competitiveness. To be successful QbD must facilitate a generic product development organization whose primary objective is to be first to file. Many R&D organizations within the generics industry are measured by the timing and number of ANDAs filed, not the quality of the ANDA. If we add the Agency’s activity in ensuring bioavailability claims during development is maintained in commercial products already approved and on the market, the risk of poor process and product understanding is tangible. In the end, the factor that may well drive the industry toward QbD may be the new pivotal guidance itself. Modeling as a foundation for product and process development will demonstrate the bottom line benefits of process understanding, making scaleup and technology transfer a smooth and effective undertaking. Consolidation in the industry will continue and the pressure to shrink the innovation timeline will only increase as competition for emerging markets and within the U.S. marketplace intensifies. In many ways the success of companies in the near future may be a direct by-product of their ability to integrate the concepts of QbD.

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