

Review Article



A Comprehensive Review on Quality by Design (QbD) in Pharmaceuticals

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Accepted on: 22-04-2013; Finalized on: 30-06-2013.

ABSTRACT

Quality by Design (QbD) refers to a holistic approach towards drug development. Quality by design is a vital part of the modern approach to pharmaceutical quality. There is much confusion among pharmaceutical scientists in generic drug industry about the appropriate element and terminology of quality by design. The purpose of this paper is to discuss the pharmaceutical Quality by Design (QbD) and illustrate how it can be used to ensure pharmaceutical quality. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include: Defining Quality target product profile, Identifying critical quality attributes, link the drug excipients attributes, establishing design space, control strategy, and product life cycle management. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. A new approach to drug development could increase efficiencies, provide regulatory support 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 required supportive data, particularly in light of the industry's current movement toward submissions based on QbD. The work also facilitates the adoption and implementation of QbD principles in the development of pharmaceutical industries. Successful implementation of QbD concepts requires cooperation across a multitude of company teams, from R&D to manufacturing to quality control and regulatory affairs. This is necessary to ensure that QbD concepts are incorporated not only when the first activities are initiated around a product's design but also during the design of the process used to make the product and other activities associated with a product's life cycle. The application of the concept of quality by design (QbD) presented in this paper aligns with the principles of ICH Q8, Q9 and Q10 guidelines.

Keywords: control strategy, critical material attributes, critical process parameters, design space, Quality by design.

INTRODUCTION

Quality by Design (QbD) was first described by Joseph M. Juran¹, and applied heavily, particularly in the automotive industry. The fundamental premise behind QbD is that quality can be “designed in” to processes through systematic implementation of an optimization strategy to establish a thorough understanding of the response of the system quality to given variables, and the use of control strategies to continuously ensure quality. The FDA has recently begun to advocate the QbD methodology for the pharmaceutical sector.²

In order to describe quality by design, we must first define what we mean by quality. In a 2004 paper, Janet Woodcock (Director for the Centre for Drug Evaluation and Research) defined pharmaceutical quality as a ‘product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer’.³

‘Quality in manufacturing is a measure of Excellence or a state of being free from defects, deficiencies, and significant variation’.

This explanation focuses on the QbD for generic drugs. The concept of QbD was mentioned in the ICH Q8 guidance, which states that “quality cannot be tested into products, i.e., quality should be built in by design”. 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 article identifies the type of data needed to address regulatory concerns and provides a pragmatic baseline for manufacturing facility requirements. Finally, it introduces new technologies that support the QbD approach. This paper describes a concise, coherent, and universal approach for determining criticality for parameters, material attributes, conditions, and quality attributes. The work also explains the risk based distinctions governing the assignment of criticality to provide consistency and facilitate the adoption and implementation of Quality by Design (QbD) principles in the development of pharmaceutical manufacturing processes. This paper describes an approach and technical process for



developing and implementing a Control Strategy, which is a planned set of controls, derived from current product and process understanding that assures process performance and product quality. Development of a Control Strategy requires a structured process, involving a multidisciplinary team of experts, linking pharmaceutical development to the manufacturing process, and engineering controls of process equipment. This paper concentrates on the techniques and principles involved in developing the early Control Strategy rather than the operational implementation of the strategy. This paper describes progress made by the Design Space within the Product Quality Lifecycle. Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions. The focus of this paper is on the technical elements of Design Space development.^{4,5}

QUALITY

“The degree to which a set of inherent properties of a product, system or process fulfils requirements” (ICH Q9)

“Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes.”

Pharmaceutical Quality by Testing

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. If they meet the manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products.⁶ Since a few tablets out of several million are tested, drug manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity, tablet hardness, etc; to ensure the outcome of in-process testing also meets the FDA approved in-process testing specifications. Manufacturers are also not permitted to make changes to the operating parameters specified in the batch record or other process changes without filing supplements with the FDA. As a result, the FDA has been overwhelmed by the number of Chemistry, Manufacturing, and Controls (CMC) supplements filed in recent years. For example, in 2005 and 2006, the FDA Office of Generic Drugs received over 3,000 CMC supplements annually.⁷⁻¹⁰ This combination of fixed manufacturing steps and extensive testing is what ensures quality under the traditional system. Limited characterization of variability, inadequate understanding to identify and quantify critical process parameters, and caution on the part of regulators leads to a very rigid and inflexible specifications that prohibit the release of products that may have acceptable clinical performance¹¹. Significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. Often these debates are

concentrated on acceptance limits or statistical aspects. FDA reviewers' conservatism results from the fact that manufacturers may not understand how drug substance, excipients, and manufacturing processes affect the quality of their products or they do not share this information with FDA reviewers. Under the traditional regulatory evaluation system, all products are treated equally without regard to the risk to the consumer.¹² This has the effect of placing too much review time on low-risk products and more significantly, takes away needed resources from the review of high-risk products. CMC review assessments of complex dosage forms (modified release products, topicals and transdermals) as well as narrow therapeutic index (NTI) drugs differ only marginally from those of simple dosage forms (many immediate release solid oral products). Further, all CMC information in applications are sometimes evaluated equally, without differentiation of criticality, resulting in the requirement of intensive resources for each application.

In summary, product quality and performance are, in the traditional framework, achieved predominantly by restricting flexibility in the manufacturing process and by end product testing. The present regulatory review system places little or no emphasis on how the design of an effective and efficient manufacturing process can ensure product quality. As a result, the complexities of process scale-up, particularly for complex dosage forms are often not recognized. Product specifications often are derived using test data from one or more batches (often not at production scale), and mechanistic understanding does not play a significant role in this process. Finally, the burdensome regulatory requirement of supplements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls inhibits continuous improvement and strategies for the implementation of continuous “real time” assurance of quality.

Pharmaceutical Quality by Design

QbD is 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 (*ICH Q8(R)*)

QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality. Thus, QbD requires an Understanding and controlling formulation and manufacturing process variables influence product quality.

Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8, Pharmaceutical Development, along with ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality Systems, indicate on an abstract level how quality by design acts to ensure drug product quality.



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.” ICH Q6A emphasizes the role of specifications stating that “Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.”¹³ 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.¹⁴ It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QbD identifies characteristics 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 the desired characteristics.¹⁵ In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient 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 1: Overview of QbD

Thus, some of the QbD elements may include,

- Define quality target product profile that describes the use, safety and efficacy of the product.
- Design and develop product and manufacturing processes.
- Identify critical quality attributes, process parameters, and sources of variability.
- Establish a control strategy for the entire process.

- Control manufacturing processes to produce consistent quality over time.

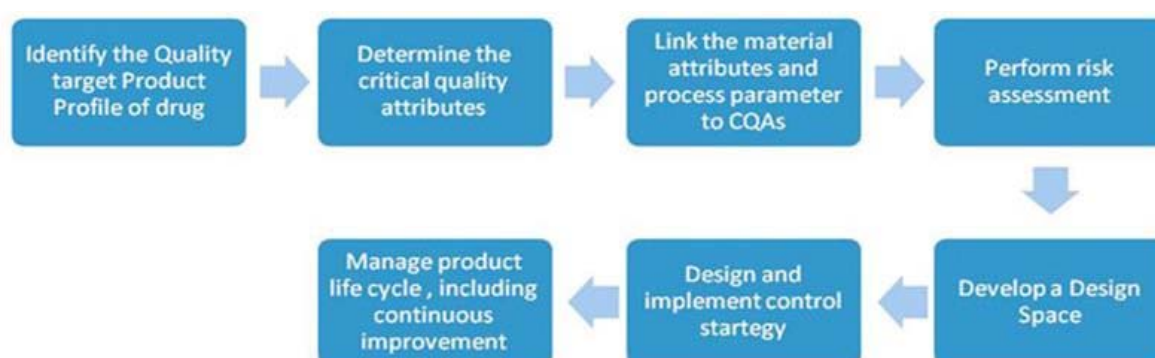
Under the QbD concept, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control. Under QbT a product specification is often set by observing data from a small number of batches believed to be acceptable and then setting acceptance criteria that required future batches to be the same. Under QbD consistency comes from the design and control of the manufacturing process and the specification of drug product under QbD should be clinically relevant and generally determined by product performance. QbD requires an understanding how formulation and process variables influence product quality. These discussions have generally focused on the development of new drugs. Drawing on these discussions and some specific aspects of the development of generic products, a QbD development process may include & begin with a target product profile that describes the use, safety and efficacy of the product & Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development & Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation & Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile & Design a manufacturing process to produce a final product having these critical material attributes & identify the critical process parameters and raw material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding & establish a control strategy for the entire process that may include raw material controls, process controls and monitors, design spaces around individual or multiple unit operations, and final product tests. The control strategy should include expected changes in scale and can be guided by a risk assessment & continually monitor and update the process to assure consistent quality Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. The difference between QbD for NDA and ANDA products is most apparent at the first step of the process. For an NDA, the target product profile is under development while for the ANDA product the target product profile is well established by the labelling and clinical studies conducted to support the approval of the reference product Table 1.

Table 1: Current Vs QbD approach to pharmaceutical development

Conventional Product Development	QbD Approach (Ideal)
Quality assured by end product testing and inspection and mainly an empirical approach.	Quality built into product & process by design, based on scientific understanding and a systematic approach.
Data intensive submission – disjointed information without “big picture”	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance requirements
“Frozen process” disallowing changes	Flexible process within design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on formulation and process robustness – understanding and controlling variation

“Quality is built in by design, not tested in”
“Quality by design is about doing things consciously.”

Key Aspects of QbD

**Figure 2:** Flow diagram (Key Aspects of QbD)

TARGET PRODUCT PROFILE (TPP)

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 labelling and links drug development activities to specific concepts intended for inclusion in the drug labelling.” 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.

The TPP is a patient and labelling centred concept, it can be thought of as the “user interface” of the drug product. Thus a generic version and its reference product would be expected to have the same TPP. A generic product may use a different formulation or design to implement the TPP. The characteristics and performance tests of a drug product would depend on the particular implementation and may differ between a generic and reference product.

For a new drug, changes to the TPP may require new safety or efficacy data.

For Reformulation, Changes to product characteristics or performance that result from a reformulation may not require that data.

Many aspects of the TPP determine the actions of formulation and process development scientists. It is the role of a pharmaceutical scientist to translate the qualitative TPP into what we define as the target product quality profile (QTPP) for further use in a quality by design process.

Identifying Quality Target Product Profile (QtpP)

“Begin with the end in mind”

By Beginning with the end in the mind, the result of development is robust formulation and manufacturing process with an acceptable control strategy that ensures the performance of the drug product.

The quality target product profile (QTPP) is “a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.” The QTPP is an essential element of a QbD approach and forms the basis of design of the generic product.

The quality target product profile (QTPP) is a quantitative substitute for aspects of clinical safety and efficacy.

International Society of Pharmaceutical Engineers (ISPE) Product Quality Lifecycle Implementation (PQLI) calls this the Pharmaceutical Target Product Profile.

Quality target product profile (QTPP) Includes, but not limited to:

- Dosage form
- Route of administration
- Strength
- Release or Delivery of the drug
- Pharmacokinetic characteristics

e.g., dissolution, aerodynamic performance

- Drug product quality characteristics for intended use e.g., sterility, purity.

Generic products would include bioequivalence to the RLD as part of the QTPP. The QTPP is not a specification because it includes tests such as bioequivalence or stability that are not carried out in batch to batch release. The QTPP should only include patient relevant product performance. For example, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size. Particle size would be a critical material attribute and thus included in the process description and control strategy. The QTPP should be performance based and not mechanism based.¹⁶⁻¹⁷

Drug Substance and Excipient Properties

Drug substance–physicochemical and biological properties in relation to product performance and manufacturability.

Excipients - concentration, characteristics and functionality in relation to product performance and manufacturability and functionality during shelf-life.

It is well recognized that excipients could be a major source of variability. Characterization and understanding of excipients' pharmaceutical properties depend on the function and utility of excipients. Drug-excipient compatibility knowledge and information are valuable in the design of formulation and manufacturing processes. Such information may be gained through theoretical investigation and experimental studies. It is known to all that mechanistic understanding of degradation kinetics provides more value in predicting stability than experimental data collected under artificial stress conditions.

Formulation Design and Development

Not all prototype formulations can be evaluated in human subjects, which mean that developing sensitive *in vitro* dissolution methods is crucial to an effective development program. FDA's recommended *in vitro* dissolution method is generally used for quality control. Generic-drug sponsors report using in-house methods for pharmaceutical development (some mentioned using as

many as five biorelevant dissolution conditions) to evaluate formulations and processes before performing bioequivalence studies.

QbD should rely on the relevance of individual studies rather than the number of studies because one of the objectives of QbD is to understand how the material attributes of the drug substance and excipients influence product quality.¹⁸

In order to design and develop a robust generic product that has the desirable QTPP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, and aqueous solubility as function of pH, hygroscopicity, and melting points.¹⁹⁻²¹

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided.

Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Overages

Use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.

Any overages in the manufacture of the drug product whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product.

Information should be provided on the-

- Amount of overage,
- Reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and
- Justification for the amount of overage.

The overage should be included in the amount of drug substance listed in the batch formula.²²

Manufacturing Process Development

Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process. Process design is the initial stage of process development, in which an outline of the commercial manufacturing processes is documented, including the intended scales of manufacturing. The outline should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during

process development are the QTPP and CQAs. Depending upon the product being developed, type of process, and process knowledge the development scientists have, it may be necessary to conduct preliminary feasibility studies before completing the process development. The selection of the type of process depends upon the formulation and the properties of the materials.

A formulation without a process is, for example, a pile of powder. Process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing.

The selection of type of process depends upon the product design and the properties of the materials. For example, tablet manufacturing typically involves one of two methods: direct compression or granulation. Direct compression is the most straightforward, easiest to control, and least expensive tablet manufacturing process. It uses two primary unit operations, mixing and compression, to produce the finished tablet. Direct compression is used when ingredients can be blended, positioned onto a tablet press, and made into a high quality tablet without any of the ingredients having to be changed. When powders are very fine, fluffy, will not stay blended, or will not compress, then they may be granulated. Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The dry granulation process is used to form granules without using a liquid solution. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling, or more typically on a roller compactor. Pharmaceutical development scientists have just begun making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing. The utility of CAPD and process simulation in drug product design is limited. This is largely because the pharmaceutical industry has traditionally put emphasis on new drug discovery and development, and the complexity of drug product manufacturing operations are not well recognized.

The use of CAPD and process simulation should result in more robust processes developed faster and at a lower cost, resulting in higher quality products.²³⁻²⁵

Identification of critical process parameters (CPPS) and critical material attributes (CMAS) and critical quality attributes (CQAS) and relationship of critical quality attribute (CQAS) to critical process parameters (CPPS) and critical material attributes (CMAS) and source of variability

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. A unit operation is a discrete activity such

as mixing, milling, granulation, drying, compression, or coating that involves physical or chemical changes. A physical, chemical, or microbiological property or characteristic of an input or output material is defined as a material attribute. Process parameters include the type of equipment and equipment settings, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The output of a process depends on the process parameters and the input material attributes. Process robustness is the ability of a process to demonstrate acceptable quality of the product and tolerate variability in inputs at the same time. The effects of variations in process parameters and input material attributes are evaluated in process-robustness studies. The analysis of these experiments identifies CPPs and CMAs that could affect product quality and establishes limits for these CPPs and CMAs within which the quality of drug product is assured. When the limits on CPPs and CMAs are scale-independent, they may form the basis of a design space as defined in ICH Q8 (R1). Even when a design space is not established, multivariate experiments are valuable because they identify CPPs and CMAs and support a conclusion of process robustness.

Process parameters and material attributes are critical when a practical change can result in failure for the product to meet the QTPP or a CQA that is outside an acceptable range. Process parameters are not critical when there is no trend to failure and there is no evidence of significant interactions within the proven acceptable range. It was necessary to conduct process robustness studies for each unit operation; The primary reason for this claim was that some generic-drug sponsors have sufficient prior knowledge to determine whether a process parameter or material attribute is critical or not and to know when process operating conditions will be robust. Process-robustness studies should be risk-based, that is, more studies with complex products and fewer studies with simple low-risk dosage forms.

A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The quality and quantity of drug substance and excipients are considered as attributes of raw materials. During process development, raw materials, process parameters and quality attributes are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical,



chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. 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. Lists typical tablet manufacturing unit operations, process parameters, and quality attributes for solid dosage forms. It should be noted that the equipment maintenance, operator training, standard operating procedure (SOP) related to the specific product manufacturing, and facility supporting systems may link to product quality directly or indirectly. Therefore, risk assessment should be used to reduce variables to be investigated. 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. In process robustness studies, effects of variations in process parameters for a candidate process are evaluated. The analysis of these experiments identifies critical process parameters that could potentially affect product quality or performance, and establishes limits for the critical process parameters within which the quality of drug product is assured. Ideally, data used to identify process parameters should be derived from commercial scale processes to avoid any potential impact of scale-up. However, in reality, these studies are often conducted on laboratory or pilot-scale batches. If results from the small scale batches have not been shown to be size independent, any conclusion from small scale studies may need to be verified in the actual commercial production batches. At the end, the effect of raw material attributes and critical process parameters on product quality or product variability is fully understood and established. Ideally, the interactions between materials attributes and critical process parameters should be understood so that critical process parameters can be varied to compensate for changes in raw materials. 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 characteristic. The most widely accepted formula for process capability is a six sigma. Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows:

Process capability index (CpK) = $\frac{\text{Upper limit of specification} - \text{lower limit of specification}}{(\sigma) \text{ standard deviation}}$

If the CpK value is significantly greater than one, the process is deemed capable. If the process capability is low, recommend an iterative five-step procedure to progressively reduce the variability of the process. These five steps are:

1. Define: The intended improvement should be clearly stated.
2. Measure: The critical product performance attributes should be measured to see if they are out of specification. The out of specification data should be analyzed and used to the sigma level of the process.
3. 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.
4. Improve: The process should be redesigned and/or process controls should be incorporated to eliminate or attenuate the significant root causes of variance.
5. Control: The improved manufacturing process should be evaluated and maintained.

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. When DOE is applied to pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. Scientists have to use prior knowledge and risk management to identify key input and output variables and process parameters to be investigated by DOE. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those that do not, as well as details such as the existence of interactions and synergies between factors. Based on the acceptable range of CQAs, the design space of CPPs can be determined. When considering scale-up, however, additional experimental work may be required to confirm that the model generated at the small scale is predictive at the large scale. This is because some critical process parameters are scale dependent while others do not. The operating range of scale dependent critical process parameters will have to change because of scale-up. Prior knowledge can play a very significant role in this regard as most pharmaceutical companies use the same technologies and excipients on a regular basis. Pharmaceutical scientists can often take advantage of past experience to define critical material properties, processing parameters and their operating ranges.²⁶⁻²⁹

IDENTIFYING CRITICAL QUALITY ATTRIBUTES (CQA)

Definition ICH Q8 (R1) defines CQAs as physical, chemical, biological or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

The International Society of Pharmaceutical Engineers (ISPE) & Product Quality Lifecycle Implementation (PQLI) defines critical quality attributes (CQAs) as physical, chemical, biological or microbiological properties or characteristics that need to be controlled (directly or indirectly) to ensure product quality.

CQA has been used by some to describe elements of the QTPP (such as dissolution) while others have used CQA to describe mechanistic factors (such as particle size and hardness) that determine product performance. Thus CQA is used to describe both aspects of product performance and determinants of product performance.

It was stated that the ICH working definition of CQA was: "A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure the product meets its intended safety, efficacy, stability and performance". This CQA definition implies that the intended safety, efficacy, stability and performance are not CQAs. Safety and efficacy clearly fall under the domain of the TPP. But if stability and performance are not CQA and not part of the TPP, then what are they? We are thus compelled to acknowledge that there is an intermediate category of product performance (or surrogates for quality) that we have defined as the QTPP.

It seems more precise to consider the TPP, QTPP, and material attributes as separate categories. The use of CQA can be reserved for cases where there is a need to refer collectively to the targets of a QbD approach. CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material.

Although many people have identified dissolution as a critical quality attribute, we consider that a set of critical material attributes (CMAs) that are independent of each other provide specific goals with which to evaluate a manufacturing process. For example a dissolution test may depend on particle size and hardness. Particle size and hardness are CMAs which can be directly linked to raw materials and manufacturing process parameters. Independent CMAs are the best way to provide a mechanistic link of the product quality to the critical process parameters in the manufacturing process. At the 2005 Drug Information Association meeting, Reed discussed dissolution in detail and indicated the greater value of has very specific CQAs. Others have commented negatively that processing behaviour of materials is usually evaluated in performance tests (flowability) rather than focusing on fundamental material properties.

Differentiating between CMAs (properties) and multifaceted performance tests is part of the movement away from quality by testing to quality by design.

The evolution of ICH Q8 is also consistent with making a distinction between CMA and performance tests. The 2004 Q8 draft put CQA and performance tests into the same pile of physicochemical and biological properties:

The physicochemical and biological properties relevant to the performance or manufacturability of the drug product should be identified and discussed. These could include formulation attributes such as pH, osmolality, ionic strength, lipophilicity, dissolution, redispersion, reconstitution, particle size distribution, particle shape,

aggregation, polymorphism, rheological properties, and globule size of emulsions, biological activity or potency, and/or immunological activity. The TPP would be the labelling statement (supported by clinical data) that the product does not dose-dump when taken with alcohol. A performance test in the QTPP would be an in vitro dissolution test in alcohol. The critical material attributes (CMA) would be the thickness of a tablet coat. Defining the CMAs on this mechanistic physical property level makes it the best link to the manufacturing process variables.²⁶⁻²⁷

CRITICAL PROCESS PARAMETERS

What is a Process Parameter?

Critical process parameter (CPP) is defined as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process uniformity. In this view, every item would be a process parameter.

We propose that process parameter be understood as referring to the input operating parameters (mixing speed, flow rate) and process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. For example, a material attribute, such as moisture content, should have the same target value in the pilot and commercial processes. An operating parameter, such as air flow rate, would be expected to change as the process scale changes.

For a given unit operation, there are four categories of parameters and attributes

- Input material attributes
- Output material attributes
- Input operating parameters
- Output process state conditions.

What is an Unclassified Process Parameter

There are many material attributes and process parameters that are important and even essential to product quality, but it is of little value to define all parameters as critical.

Thus we propose three categories for attributes or parameters:

1. Unclassified,
2. Critical and
3. Non-critical

For example, in the granulation process, the impeller speed should clearly be identified as an unclassified

process parameter because if impeller speed were zero the process step would not be successful. However, this does not mean that impeller speed is always a critical parameter. If development studies demonstrated the granulation was not affected by realistic changes in impeller speed, it would not be identified as critical.

What is a Critical Process Parameter

A parameter is *Critical* when a realistic change in that parameter can cause the product to fail to meet the QTPP.

Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider.

A simple example is that an impeller speed of zero will always fail.

Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest to the sponsor for each process parameter. The POS can also be considered as the extent of the sponsor's quality system with respect to these parameters. This definition is at the discretion of the application that sponsor must balance the trade-offs in its definition. The POS defines the scope of the application and the sponsor's quality system so that going outside of the POS must need an amendment or supplement to the application. Thus sponsors benefit from defining a large feasible POS. The cost of a large POS is the need for the pharmaceutical development (in the

form of prior knowledge, process models or experimental data) to cover the POS and the increased chance that a parameter will be found critical in the large POS. The only constraint on the narrowness of the POS is that the POS must encompass the variability of the process parameters around their target values.

Our criteria for identifying critical and non-critical parameters are that a parameter is *Non-critical* when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range (PAR)(see explanatory footnote on first page of article), which is the range of experimental observations that lead to acceptable quality. A sponsor has the option of conducting experimental observations over the entire POS; in this case the POS could be equivalent to the PAR. Alternatively a sponsor may use prior knowledge, mechanistic models and trends from the PAR to draw conclusions about sensitivity over a POS that is larger than the PAR. If the lack of interaction part of the test cannot be met, then the parameter remains a UPP.

A parameter is critical when there is an observation of failure or a trend to failure predicted within the POS. If the interaction between two parameters is significant enough to predict a potential failure in the POS, then both parameters should be considered as critical. The most definitive way to identify critical and noncritical parameters is by scientific investigations involving controlled variations of the parameters.

Table 2: Classification of Process Parameters

Parameter Type	Definition	Sensitivity
Non-Critical Process parameter (Non-CPP)	Not critical	No failure in target product quality profile (TPQP) observed or predicted in the (non-CPP) potential operating space (POS),
		No interactions with other parameters in the proven acceptable range (PAR)
Unclassified Process parameter (UPP)	Criticality unknown	Not established
		The default in the absence of pharmaceutical development
Critical Process parameter (CPP)	Critical (control needed to ensure quality)	Failure in target product quality profile (TPQP) observed or predicted in the potential operating space (POS), or
		Interactions with other parameters in the proven acceptable range (PAR)

Uniqueness of Critical Process Parameters

Because of the broadness of the CPP definition it is possible for two investigators to examine the same process and come to a different set of CPP. The set of CPP is not unique, but the chosen set must be sufficient to ensure product quality. Different sets of CPP can have several origins. One is that the definition of operating parameters depends on the engineering systems installed on a piece of process equipment.

Example, one fluid bed dryer may define the product temperature as an operating parameter and have an internal control system (a thermostat) that maintains that temperature, while another fluid bed dryer may have

inlet air flow rate and inlet air temperature indicated as operating parameters.

Batch record for the first unit might indicate a fixed temperature, while the second unit would have a design space that indicated the combination of inlet air flow rate and inlet air temperature that would insure the appropriate product temperature.³⁰

RISK ASSESSMENT AND DESIGN SPACE

Quality Risk Management (ICH Q9) indicates that, the manufacturing and use of a drug product necessarily entail some degree of risk.



Risk assessment is a valuable science based process used in science-quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs.

Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data.

Use of a risk assessment tool:

A cross-functional team of experts could work together to develop an Ishikawa (fishbone) diagram that identifies potential variables which can have an impact on the desired quality attribute

ICH Q8 (R1) defines **Design space** as, the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.

Many believe design space and QbD are interchangeable terms. This is incorrect. For generic-drug applications, design space is optional. QbD can be implemented without a design space because product and process understanding can be established without a formal design space. It should be pointed out that implementation of QbD is strongly encouraged by FDA. For some complex drug substances or drug products, implementation of QbD is considered a required component of the application.

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs. It describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should include their linkage to or across unit operations. Such relationships are arrived at by iterative application of risk assessment and experimental design, modelling, as well as the use of literature and prior

experience. The Design Space also contains the proven acceptable ranges (PAR) for CPPs and acceptable values for their associated CQAs. Normal operating ranges are a subset of the Design Space and are managed under the company Pharmaceutical quality System. The Design Space may also contain operating ranges for process parameters classified in the intermediate criticality category discussed previously. Information regarding site and scale of manufacture may also be included, depending on the quality of the process knowledge upon which the Design Space is based.

In the presence of interacting critical process parameters a design space is one approach to ensure product quality although it is not a check-box requirement.

The current definition of design space is “The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.”

This definition evolved from early ICH Q8 drafts where design space was defined as “the established range of process parameters that has been demonstrated to provide assurance of quality”. The change emphasizes the multidimensional interaction of input variables and closely binds the establishment of a design space to a conduct of a DOE that includes interactions among the input variables.

A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process.

Submission of a design space to FDA is a pathway obtaining the ability to operate within that design space without further regulatory approval.³¹⁻³⁵

Scale-Up

Currently, the mechanistic understanding of pharmaceutical unit operations is limited. Scale-up is largely based on general rule-of-thumb and trial-and-error approaches. During scale-up, process parameters may vary while material attributes will not. QbD offers many more advantages for complex products than for simple ones. It was noted that scale-up can be done without QbD, but with much higher risk.

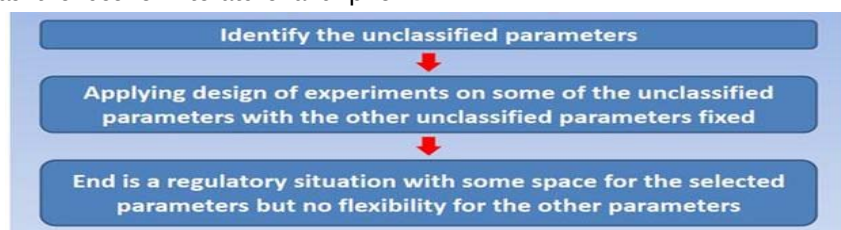


Figure 3: Steps to Design Space

DEFINING CONTROL STRATEGY

ICH Q8 (R1) defines control strategy as:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

The controls can include parameters and attributes related to:

- Drug substance,
- Drug-product materials and components,
- Facility and equipment operating conditions,
- In-process controls,
- Finished-product specifications,
- The associated methods and
- Frequency of monitoring and control. (ICH Q10)

Specifically, the control strategy may include:

- Control of input material attributes (e.g., drug substance, excipients, and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specifications
- Practical controls
- Facility controls, such as utilities, environmental systems and operating conditions
- 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)
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

The Control Strategy should establish the necessary controls - based on patient requirements - to be applied throughout the whole product lifecycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution.

Minimal and enhanced approaches

As in ICH Q8(R), a distinction may be drawn between a minimal and an enhanced control strategy approach.

In a *Minimal Control Strategy*, drug product quality is controlled primarily by intermediate (in process material) and end product testing.

In an *Enhanced Control Strategy* drug product quality ensured by risk-based control strategy for well understood product and process, and quality controls are shifted upstream, with the possibility of real-time release or reduced end-product testing.

Developing the control strategy

Development of a Control Strategy requires a structured process, involving a multi-disciplinary team of experts, linking pharmaceutical development to the manufacturing process, and engineering controls of process equipment.

The PQLI Control Strategy Team has proposed a Control Strategy Model that facilitates understanding and that may be used as a cross-functional communication tool.

Personnel at all levels should be able to understand the way control strategy links from CQAs to operational aspects to ensure, for example that:

- Chemists understand in-process controls are established to keep the process inside the design space and seek opportunities for simplification of controls, as knowledge is gained.
- Engineers know how equipment operating conditions impact product quality.
- Quality Assurance professionals know where the highest risks are in the process.

Although the primary driver for development of a control strategy will be assurance of product safety, efficacy and quality, the Control Strategy may also ensure the meeting of other business objectives such as operator health and safety, protection of the environment, manufacturability, and supplies related issues, efficiency, and profitability. Development of a Control Strategy for a product will therefore be a structured activity involving a multi-disciplinary team of experts. This team may include representatives from formulation development, drug substance development, process development, analytical development, QC, QA, Regulatory Affairs, manufacturing, engineering, and specialists in Process Analytical Technology (PAT) and chemo-metrics.

A Control Strategy and a product release strategy are not the same, but demonstration of adherence to the Control Strategy would support the product or batch release strategy.

Control of input material attributes

Variability in the manufacturing processes may be caused by variability in the drug substance and raw materials and their attributes, when linked to a CQA. The impact of not only chemical but also physical material attributes and their variability need to be understood. For example, for an oral solid dosage product, impact of factors such as particle size distribution, particle shape distribution, density, surface area, surface energy, flow, cohesiveness, friction, elastic modulus, amorphous content, compactibility, hygroscopicity, solubility, and static charge should be assessed. A linkage between the product CQAs and the input material attributes should enable identification and understanding of the most critical material attributes and their impact on the product CQAs. Controlling the variability of input materials can be

managed in different ways, e.g. by functional specifications (not necessary in concurrence with compendia specifications) or by managing the variability directly in the process using closed loop controls. One example is raw materials affected by seasonal variations in the moisture level and used in a moisture critical blend. By applying PAT tools such as NIR (Near Infrared) spectroscopy, drying can be monitored on-line and the drying process controlled to the end-point with a closed feed-backward control loop in place. In many cases the variability in a material input can be managed by operating the process conditions differently within the Design Space. Other input materials such as packaging material should be studied during development to identify and understand which material attributes impact the manufacturing process and final product CQAs.

Real-time testing / In-process controls

Real time testing is needed to base the release the product on product and process understanding rather than on end product testing alone or on result of batch analysis.

Real time testing include all controls that need to be performed during processing, including control of Critical Process Parameters, in-process material attributes and components, as well as equipment and facility parameters that must be monitored or controlled to achieve the product CQAs.

Controlling the Critical Process Parameters during processing is important as they have a direct impact on the CQAs, but other parameters, that have an impact on downstream processing or other end-product quality attributes not already covered by a CQA, should be monitored or controlled as well. Which parameters to monitor or control is the outcome of Quality Risk Management (QRM) activities aimed at mitigating the risks arising during manufacturing.

In-process controls could include

- conventional sampling and
- At-line analysis or On-line or in-line univariate sensors or multivariate probes (typical spectroscopy)

They may be manual or automated, depending on the nature of the process itself, what needs to be measured and controlled, how often, scale, process time, and the nature of the manufacturing equipment.³⁶⁻³⁷

Control strategy and the product lifecycle

The Control Strategy is related to the level of process understanding at a given time, and evolves as manufacturing experience increases.

The originally specified measures, controls or models may be modified or even removed, or the need for additional controls may be identified.

Other revisions to the Control Strategy may relate to continual improvement, for example the introduction of improved analyser or control technology.

Periodic reviews of risk assessments and mitigation should be conducted to determine the appropriateness of the Control Strategy based on product manufacturing history.

Failure or deviations should be investigated and the effectiveness of the control system considered in relation to the identified root cause.

Corrective and preventive actions should be applied and the Control Strategy updated as necessary (including any regulatory actions required) in the light of new product and process knowledge.

Implementing PAT in the Control Strategy will require the application of process models (multivariate prediction models) that either predicts CQAs or CPPs or a combination of both. These models may require frequent updates, depending on the maturity of the model (e.g., the amount of data and their variability within the model), as well as the kind of data that has been included to reflect variability in scale, equipment, analytical set-up, sampling, and site.

A monitoring program for verifying the validity of process models should be established and be based on a risk analysis of the model itself and include possible ways to verify the model by other means. One example would be to compare the predicted CQA value to a conventional analytical method. The monitoring program should include requirements for when a model has to be updated (e.g. change of raw material supplier or deviations resulting in increased knowledge).

Continuous Improvement

“Continuous improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics.”

QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability.

The backbone for Continuous Improvement is the Pharmaceutical Quality System. PQS should facilitate continual improvement and help to: “Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently.

Quality risk management can be useful for identifying and prioritizing areas for continual improvement. “Continuous improvement is not the same as corrective actions preventative actions (CAPA). CAPA’s occur when product

quality characteristics are in question (e.g., out of specification). For continuous improvement efforts, products should already be in compliance with their specifications and process improvement steps should be within the original "design space"

Examples of Continuous Improvement include adjusting a set point of a process, advanced control techniques, new equipment of the same design, re-designing a process step, changing a working process, LEAN initiatives, simplifying documents, automating a process, installing on-line measurements, removing a unit operation, changing the design space and updating the Control Strategy.³⁸

"Continuous Improvement is Hallmark of QbD".

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Source of Support: Nil, **Conflict of Interest:** None.