

## Short review on Quality by design: A new Era of Pharmaceutical drug development

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### Abstract

The purpose of present article is to discuss the concept of pharmaceutical Quality by Design (QbD) and describe how it can be help to ensure pharmaceutical quality. Quality by design is an essential part of the modern approach to pharmaceutical quality. The elements of quality by design are examined and a consistent nomenclature for quality by design, critical quality attribute, critical process parameter, critical material attribute, and control strategy is proposed. The use of QbD was contrasted with the evaluation of product quality by testing alone. 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 target product quality profile, designing product and manufacturing processes, identifying critical quality attributes, process parameters, and sources of variability & controlling manufacturing processes to produce consistent quality over time. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables.

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### 1. INTRODUCTION

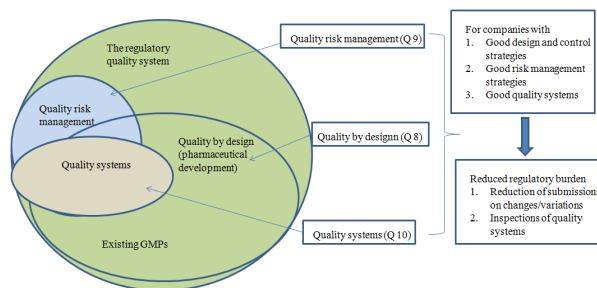
Over the past few years, pharmaceutical companies have been facing an increasingly difficult economic climate. An increase in the regulatory hurdles for the approval of new molecular entities, patent expirations and increased healthcare costs have resulted in more focus in the costs associated with the manufacturing and development of pharmaceuticals. It has been estimated that many pharmaceutical processes operate at 2.5–4.5 sigma quality levels, but resource intensive pharmaceutical company quality systems achieve 5 sigma quality

levels by sorting, reworking, and so on to prevent defective product leaving the factory [1]. During the heydays of the pharmaceutical industry, there was lesser focus on the yields, number of defects, etc., and the quality organizations of the companies were more focused on compliance based on inspection of the final products. Traditional development focused on the formulation and the delivery of the product to the next phase of the clinical studies. Most of the formulation development tended to be iterative and empirically designed. Thus, changes were driven by the need to modify the process during scale-up or due to the formulation failing to meet the desired shelf life of the product.

During phase 3, changes were kept to a minimum to avoid the need for expensive bioequivalence studies to bridge between the Clinical Trial Material (CTM) and the commercial product. Thus, manufacturing processes were fixed and the quality of the product was measured by end product testing (commonly referred to as quality by testing). In this case, quality is not built in to the product and is achieved by end product testing. This approach is inefficient and does not facilitate continual improvement. In the past, there also existed a notion that the regulatory processes and requirements prohibited manufacturing enhancements, which in turn prevented the modernization of the pharmaceutical industry. The initiation of the cGMPs for the 21st Century Initiative [2] and the publication of the Process Analytical Technology (PAT) guidance [3] in 2004 by the FDA paved the way for the modernization of the pharmaceutical industry.

In July 2003, the experts from the three regional grouping (USA, EU, and Japan) working on the Quality Topics within ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) created a vision for the future pharmaceutical quality system (Figure 1). This vision recognizes that regulatory agencies will also benefit from this

initiative as it will enable them to prioritize and allocate resources more efficiently, and patients will also benefit from improved access to medicines and an enhanced assurance of quality.



**Figure 1:** ICH vision for the future pharmaceutical quality system

“Quality by design (QbD),” although a new concept to the pharmaceutical industry, is a tried and tested concept that has been in existence for quite a few years and has been extensively applied in the automotive, the semiconductor, and the petrochemical industry. The concept of building quality into products has been extensively documented by Deming and Juran. The common theme of the various initiatives is “planning for quality,” that is, building quality into the products compared to the traditional paradigm of testing the product to ensure quality. The Juran trilogy concept identifies quality planning, quality control, and quality improvement as three fundamental aspects of quality planning [4]. Quality planning is the process of identifying the needs of the customer and designing the product and the process to meet the needs of the customer.

## 2.0 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 [5]. A brief description of the

two enablers and their utility is provided in the following sections.

### 2.1 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.

### 2.2 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.

### 3.0 ELEMENTS OF QUALITY BY DESIGN

ICH Q8(R2): 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 2 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.

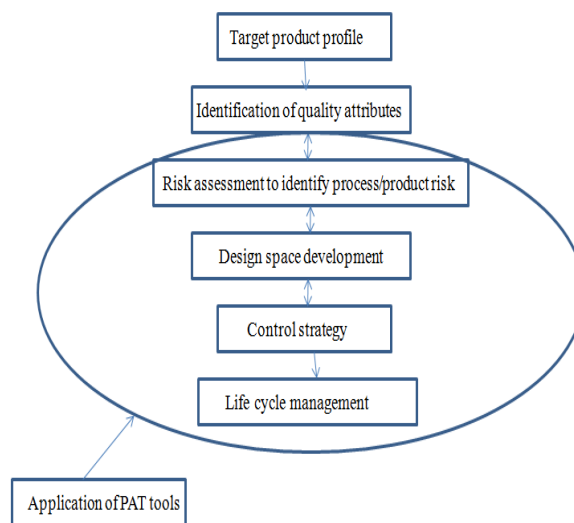


Figure 2: Elements of quality by design

### 3.1. Identifying a Quality Target Product Profile (QTPP):

The quality target product profile (QTPP) as defined in ICH Q8(R1) [6, 7] is a summary of the quality characteristics or attributes of a drug product that ideally will be achieved and thereby ensure the safety and efficacy of a drug product. The QTPP forms the basis of design for the development of the product and is developed with the end in mind. It is both prospective, that is, it describes the goals for the development team, and dynamic, that is, the QTPP may be updated or revised at various stages of development as new information is obtained during the development process. The FDA has published a guidance defining the Target Product Profile (TPP) [8], that focuses on the consumer (patient) and the desired product label. The QTPP is a subset of the TPP and is more oriented towards the chemistry, manufacturing and controls (CMC) aspects of development.

### 3.2. Identification of Critical Quality Attributes

Pharmaceutical development consists of product and process design and development. The TPP provides the basis for the ideal dosage form. While designing a product and process, it is important to focus on the clinical performance, manufacturability, and global acceptability of the drug product. In the QbD paradigm, it is imperative that the manufacturing process is capable of accommodating typical variability in the inputs, resulting in a product that always meets the requirements of the QTPP.

**3.2.1. Critical Quality Attributes (CQA):** A critical quality attribute as defined by ICH Q8(R2) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally

associated with raw materials (drug substance, excipients), intermediates (in-process materials), and drug product. Drug product CQAs derived from the QTPP are used to guide the product and process development. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy. Depending on the CR dosage form, these may include the aspects affecting the purity, potency, stability, drug release, microbiological quality, and so on. CQAs can also include those properties of a raw material that may affect drug product performance or manufacturability. An example of this would be drug substance particle size distribution (PSD) or bulk density that may influence the flow of a granulation and therefore the manufacturability of the drug product. Similarly, the dissolution from a controlled release dosage form is dependent on the particle size of the polymer and the hardness of tablet. In this example, PSD and hardness can be designated as CQA's. They are also commonly referred to as critical material attributes (CMA). Table 1.

**Table 1:** Example of QTPP for a Typical Oral Controlled Release

Summary Quality Target Product Profile and Identification of Critical Quality Attributes for a Typical Oral Controlled Release Product		
Quality Attribute	Target	Criticality
Dosage form	Dosage form could be matrix tablet, maximum weight XX mg	
Potency	Dosage form label claim	
Dosing	One tablet per dose, once daily	
Pharmacokinetics	For example, controlled release over a period of 12 or 24 hr	Related to dissolution
Appearance	Dosage form description	Critical
Identity	Positive for drug name	Critical
Assay	95.0-105.0%	Critical
Impurities	List specified impurities with appropriate limit; unspecified impurities with limit; total impurities with limit	Critical
Water	Current limit (eg., NMT 1.0%)	Critical/Not critical depending on API sensitivity to moisture
Content Uniformity	Meets USP/EP/other pharmacopoeia	Critical
Hardness	NLT X SCU (preferred for film coating) for a tablet	For example, can be critical if related to dissolution
Friability	Current limit (eg., NMT 1.0%)	
Dissolution	Conforms to USP (eg., use a 5 point profile or NLT 10% in 0.1 N HCl for enteric coated tablets)	Typically critical
Microbiology	If testing required, meets harmonized ICH criteria	Critical only if drug product supports microbial growth

**3.2.2. Quality Attributes Important to the Performance of the Drug Product:**

From a clinical perspective, safety and efficacy (product performance) is of prime importance. Thus, for an oral CR product, it is important to consider attributes that are potential surrogate(s) for performance. This may be drug dissolution/release, potency, polymer concentration, polymer viscosity, glass transition temperature (Tg) of composite, etc., or any other attribute that can either be substituted for drug release or clinical design space.

**3.3. Quality Risk Assessment:**

A key objective of risk assessment in pharmaceutical development is to identify which material attributes and process parameters affect the drug product CQAs, that is, to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the CQAs are within the desired requirements.

The identification of critical process parameters (CPP) and critical material attributes is an iterative process and occurs throughout development. During the initial phases of development, prior knowledge serves as the primary basis for the designation as there is not sufficient process/product understanding on the product under development. Therefore, the risks identified at the initial phases are perceived risks and as further process/product understanding is gained, the actual risks become clearer and a control strategy can be better defined. The risk assessment tools used in earlier phases of development therefore tend to be more qualitative and serve as a means to prioritize the experimentation. Typical tools used include risk ranking and filtering, input–process–output diagrams, Ishikawa diagram, and so on. Risk filtering and ranking is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative

and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. Table 2 is a typical example of risk filter that is used in early development to prioritize parameters/attributes with higher risk. This is typically qualitative in nature.

**Table 2:** Example of risk filter during initial drug development

Initial risk assessment DP QRA, showing the impact of critical parameters/attributes/process and its impact on the CQA								
Critical parameters factors DP CQA	Polymer	Roll gap/ Roll force (ribbon dosisiv)	Compressio n force	Amount of fine after RC	Lubricant distribution	Process speed	API PSD	Precompres sion force
Appearance	Low	Low	High	Low	High	Low	Low	Low
Identity	Low	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	High	Low	Low
CU	Low	Medium	Low	Low	Low	Low	Low	Low
Impurity	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	High	Low	Low	Low	Low	Low	Low	Low
Tablet Hardness	High	High	High	High	High	High	Low	High
Friability	High	High	High	High	Low	Low	Low	Low
Yield	Low	Low	Low	Low	Low	Low	Low	Low

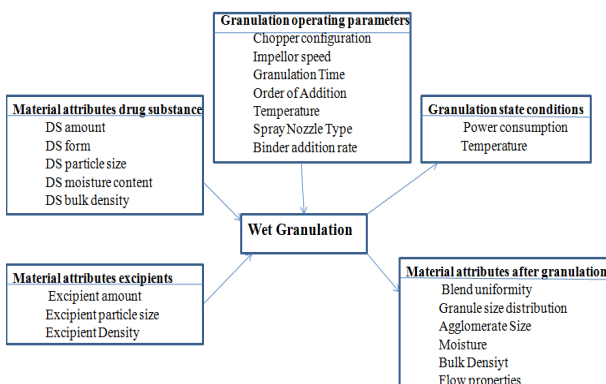
Several other tools are also available that help to prioritize the attributes/variables [9]. Some of these include Preliminary Hazard Analysis (PHA), Fault Tree Analysis (FTA), Hazard and Operability Analysis(HAZOP), Hazard Analysis and Critical Control Points (HACCP), Root cause Analysis (RCA), Decision Trees (DT), Probabilistic Risk Analysis (PRA), and so on.

**4. CRITICAL PROCESS PARAMETERS**

**4.1. Process Parameter**

There is confusion about what is a process parameter. Previously, some have defined a critical process parameter (CPP) 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 consistency. In this view, every item in Figure 3 would be a process parameter.



**Figure 3:** An example of identification of process parameters and material attributes prior to pharmaceutical development

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

#### 4.2. Unclassified Process Parameter

We recognize that 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: unclassified, critical, or non-critical. The criticality of an unclassified parameter is undetermined or unknown. Sponsors' pharmaceutical development studies can provide the additional data needed to classify an unclassified parameter as critical or non-critical. For a process or dosage form we expect wide agreement on the set of attributes or parameters that need classification. Prior experience and standard texts will guide this process. 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. An application that did not include the results of pharmaceutical development studies investigating the criticality of the UPP would have a large number of UPP remaining in the final submission.

#### 4.3. Critical Process Parameter

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. 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. Table 3 summarizes the proposed classification of process parameters.

**Table 3:** Classification of Process Parameters

Parameter type	Definition	Sensitivity
Non-critical process parameter (non-CPP)	Not critical	<ul style="list-style-type: none"> <li>No failure in target product quality profile (TPQP) observed or predicted in the potential operating space (POS), and</li> <li>No interaction with other parameters in the proven acceptable range (PAR)</li> </ul>
Unclassified process parameter (UPP)	Critically unknown	<ul style="list-style-type: none"> <li>Not established</li> <li>The default in the absence of pharmaceutical development</li> </ul>
Critical process parameter (CPP)	Critical (control needed to ensure quality)	<ul style="list-style-type: none"> <li>Failure in target product quality profile (TPQP) observed or predicted in the potential operation space (POS), or</li> <li>Interactions with other parameters in the proven acceptable range (PAR)</li> </ul>

## 5. CONTROL STRATEGY

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 filing 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.

## 6. CONCLUSIONS

Quality by design is an essential part of the modern approach to pharmaceutical quality. This paper clarifies the use of QbD including:

1. Emphasis on the importance of the Target Product Quality Profile in articulating a quantitative performance target for QbD.
2. Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process.
3. Clarification that critical process parameters are operating parameters and should be combined with critical material attributes to describe the relation between unit operation inputs and outputs.
4. A definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes
5. The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice.
6. An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs.

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