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QUALITY BY DESIGN (QBD): AN EMERGING PARADIGM FOR DEVELOPMENT OF PHARMACEUTICALS

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ABSTRACT

Quality by Design (QbD) refers to a holistic approach for development of quality pharmaceutical products, it is an essential part of the modern approach to pharmaceutical quality, QbD is 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), Quality Target Product Profile (QTPP)] 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. 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), Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), Critical Process Parameter (CPP), Process Analytical Techniques (PAT).

INTRODUCTION

The concept of "Quality by Design" (QbD) was defined as an approach which covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment. QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing processes to maintain the prescribed product quality. Guidelines and mathematical models are used to ensure the establishment and use of the knowledge on the subject in an independent and integrated way. Within this vision, the key framework guidance documents ICH Q8 Pharmaceutical Development and ICH Q9 Quality Risk Management were published in 2005 and ICH Q10 Pharmaceutical Quality System followed these documents in 2008. [15] Incorporating QbD in the early stages of product development can lead to a product that is easy for scale up with fewer challenges and obstacles at pilot and commercial scale manufacturing. According to ICH Q8 guidance, "Quality cannot be tested into products, i.e. quality should be built in by design."[3] Process and the critical process parameters to be controlled in order to reach the new building block which is the

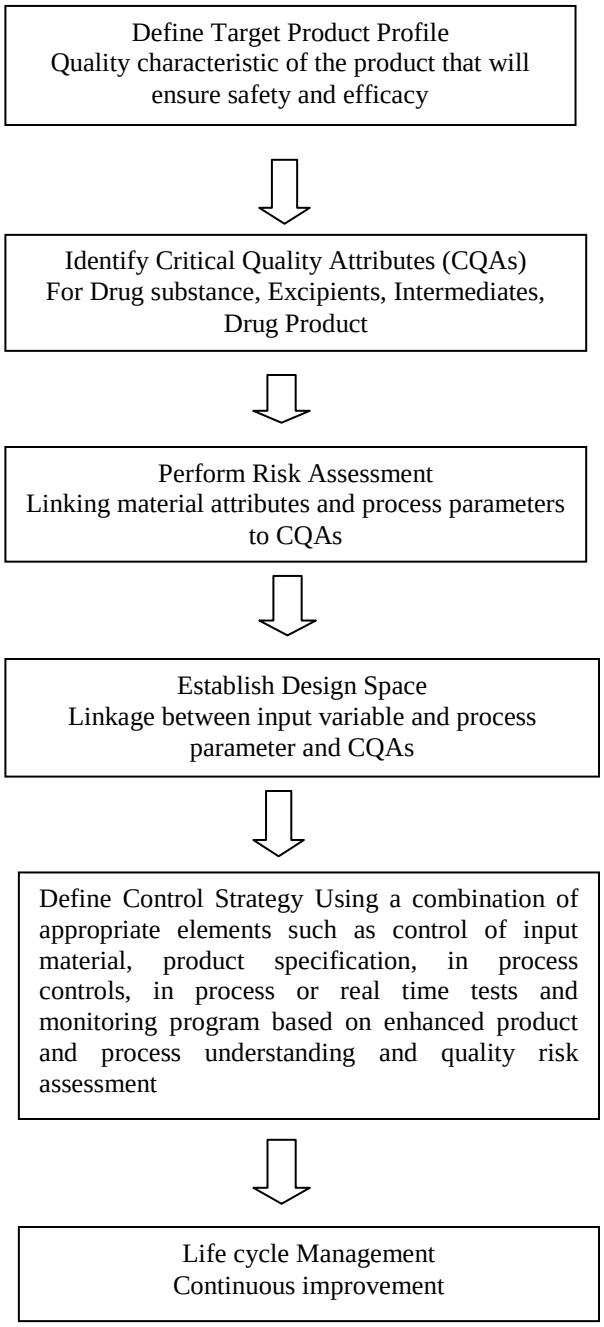
expectation of variances within those critical process parameters that can be accepted. This approach allows the establishment of priorities and flexible boundaries in the process. In order to initiate a successful QbD program, the first step is to identify those process parameters that are essential to product quality and develop well – validated analytical methodologies to monitor those parameters. [10, 12]
The cGMP initiative described a "Desired State." for pharmaceutical manufacturing through QbD in which:

- Product quality and performance are achieved and assured by design of effective and efficient manufacturing processes.
- Product specifications are based on a mechanistic understanding of how formulation and process factors impact product performance.
- Manufacturers have the ability to affect continuous improvement and continuous "real time" assurance of quality.
- Regulatory policies and procedures are tailored to recognize the level of scientific knowledge supporting product applications, process validation and process capability.
- Risk-based regulations are commensurate with the level of scientific understanding of how formulation and manufacturing process affect product quality and performance, and the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product. [9,14,19]

The concept of building quality into products has been extensively documented by Demingb 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. 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. [8, 11]

Comparison of the traditional and current of QbD as described in table 1. [1, 18]

Steps of QbD: [4, 6]



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. [16]

Quality Target Product Profile (QTPP): Quality Target Product Profile (QTPP) 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. 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. Quality Target Product Profile (QTPP) 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 QTPP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. QTPP is related to identity, assay, dosage form, purity, stability in the label. For example, a typical QTPP of an immediate release solid oral dosage form would include

– Tablet Characteristics
– Identity
– Assay and Uniformity
– Purity/Impurity
– Stability, and
– Dissolution

The QTPP 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 QTPP 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. [5, 6]
Based on the clinical and pharmacokinetic (PK) characteristics as well as the in vitro dissolution and physicochemical characteristics of the RLD, a quality target product profile (QTPP) was defined for Generic Acetriptan Tablets, 20 mg as described in table 2. [20]

Critical quality attributes (CQA): Critical quality attribute (CQA) 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 are the properties that are important for product performance, that is, the desired quality, safety, and efficacy. For example Depending on the Control Release 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. [2, 11, 17] Table 3 summarizes the quality attributes of generic acetriptan tablets and indicates which attributes were classified as drug product critical quality attributes (CQAs). For this product, assay, content uniformity (CU), dissolution and

degradation products are identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, will be investigated and discussed in detail in subsequent formulation and process development studies. On the other hand, CQAs including identity, residual solvents and microbial limits which are unlikely to be impacted by formulation and/or process variables will not be discussed in detail in the pharmaceutical development report. However, these CQAs are still target elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy. [20]

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.

What is a 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 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?

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. Table 4 provides an identification of unclassified process parameters (UPP) at the beginning of a development process. These UPP may later be classified as critical or noncritical. [11] 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.

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), 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. The focus in the process development report is on the additional studies that build this knowledge. These studies can be conducted on pilot or lab scale and do not need to be conducted under current Good Manufacturing Practice. When the sensitivity of process parameters is established, this can be used to design appropriate control strategies. However, it may not be possible (due to economic and time constraints) to conduct scientific investigations on all UPP. We believe that prior knowledge and experience with the unit operations can be used to classify some UPP. The prior knowledge can be used in a formal risk assessment process to prioritize unclassified parameters for further experimental study. This is potentially a challenging issue for FDA review, if the reviewer does not agree with the risk assessment used to classify parameters as non-critical, then all further conclusions may be in doubt because a potential critical variable was left out of the experimentation that was used to develop a design space.

Our criteria for identifying critical and non-critical process parameters are based on the sensitivity of product characteristics to changes in the process parameters. Other approaches presented in the literature link the classification as critical to the variability in a process parameter. The variability of a process parameter impacts the control strategy that will be used, but we concur with ISPE PQLI that control of a variable does not render it non-critical. 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. For 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. The 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. Another source of differences in the set of CPP comes from the balance between control of operating parameters and material attributes. Morris indicates that set of CPP and CMA (which he refers to as process critical control points (PCCP) can affect the scale up process. [6, 13]

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. 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. Manufacturers 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. [11]

Process Analytical Techniques (PAT): QbD combined with Process Analytical Technology (PAT) tools enable process control and increase the assurance that product quality attributes are achieved consistently, and/or that manufacturing efficiencies are obtained. PAT is one of the many tools or enablers of QbD. PAT can be an invaluable tool through life cycle management. During product and process development it can enhance prior knowledge and improve process understanding, help with process mapping and monitoring, model building and along with QRM, help establish a design space and a control strategy. During manufacturing operations PAT can help ensure process robustness and consistent output, as well as enabling operational flexibility through adaptive process controls, based on process understanding, and ultimately Real Time Release (RTR) through a science/risk based approach and Quality Systems. For continual improvement, PAT tools, such as multivariate data analysis and process control systems, enable historical data tracking and trending for continual improvement and consistent patient outcome. [1, 7]

CONCLUSION

Quality by design is an essential part of the modern approach to pharmaceutical quality. This paper discusses the pharmaceutical QbD and describes the emphasis on the importance of the Quality Target Product Profile in articulating a quantitative performance target for QbD, identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process, 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, a definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes, the role of the control strategy as the mechanism for incremental implementation of QbD elements into practice.

Table 1: Comparison of the traditional and current QbD approaches

	Traditional Approach	QbD Approach
Broad Concept	Quality decisions 'divorced' from science and risk evaluation. *Adherence to filing commitments.*	Quality decisions and filing commitments *based on Process Understanding and Risk Management. Design Space concept.*
Quality	Post-manufacture sampling and quality testing. *Process Validation.*	Management of variability. Process control focused on critical attributes. *Continuous Quality Verification.*
Systems	Systems designed to inhibit changes & minimize business risks. *Discourages improvement & innovation*	Changes managed within company's quality system. Real time batch release feasible. *Higher reliance / trust / understanding on systems.*
Regulatory	Compliance focus. *Changes require prior approval, lengthy process, and uncertain outcome.*	Regulatory scrutiny adjusted to level of Process Understanding. *Continuous improvement allowed within Design Space.*

Table 2: Quality Target Product Profile (QTPP) for Generic Acetriptan Tablets, 20 mg

QTPP Elements	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design	Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration	Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength	20 mg	Pharmaceutical equivalence requirement: same strength

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

Table 3: Critical Quality Attributes (CQAs) of Generic Acetriptan Tablets, 20 mg.

Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Colour and shape acceptable to the patient. No visual tablet defects observed.	No	Colour, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odour	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the acetriptan tablet
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer

			complaints.
Identification	Positive for acetriptan	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay	100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development
Content Uniformity (CU)	Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.
Dissolution	NLT 80% at 30 minutes in 900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.
Degradation Products	ACE12345: NMT 0.5%, Any unknown impurity: NMT 0.2%, Total impurities: NMT 1.0%	Yes	Degradation products can impact safety and must be controlled based on compendial/ICH requirements or RLD characterization to limit patient exposure. ACE12345 is a common degradant of acetriptan and its target is based on the level found in near expiry RLD product. The limit for total impurities is also based on RLD analysis. The target for any unknown impurity is set according to the ICH identification threshold for this drug product. Formulation and process variables can impact degradation products. Therefore, degradation products will be assessed during product and process development.
Residual Solvents	USP <467> option 1	Yes*	Residual solvents can impact safety. However, no solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. Therefore, formulation and process variables are unlikely to impact this CQA.
Water Content	NMT 4.0% w/w	No	Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. However, in this case, acetriptan is not sensitive to hydrolysis and moisture will not impact stability.
Microbial Limits	Meets relevant pharmacopoeia criteria	Yes*	Non-compliance with microbial limits will impact patient safety. However, in this case, the risk of microbial growth is very low because roller compaction (dry granulation) is utilized for this product. Therefore, this CQA will not be discussed in detail during formulation and process development.

*Formulation and process variables are unlikely to impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the drug product profile and should be addressed accordingly.

Table 4: Classification of process parameter

Parameter type	Definition	Sensitivity
Non-critical process parameter (non- CPP)	Not critical	-No failure in target product quality profile (QTPP) observed or predicted in the potential operating space (POS), and -No interaction with other parameters in the proven acceptable range (PAR)
Unclassified process Parameter (UPP)	Critically 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 (QTPP) observed or predicted in the potential operation space (POS), or -Interactions with other parameters in the proven acceptable range (PAR)

REFERENCES

1. Mandenius, Carl-Fredrik. Biotechnology Journal, 2009; 4(6): 1-28.
2. ISPE. Overview:Quality by Design, 2008: 1-3.
3. Woodley BioReg Limited. The evolution of QbD-From inception to maturity in 2012, 2012; 9:5- 8.
4. Patil AS, Pethe AM. Quality. Int J of Pharm Quality Assurance, 2013; 4(2): 13-9.
5. Roy S. Int J Pharm Biomed Res, 2012; 3(2): 100-08.
6. Trivedi B. Int J of pharm and pharm sci, 2012; 4(1):17-29.
7. Hernandez-Abad PE, Huang J, Romero-Torres S. European Pharmaceutical Review, 2009; 4: 55-8.
8. Quality by Design (QbD) Based Method Development for the Determination of Impurities in a Peroxide Degraded Sample of Ziprasidone, Water Corporation. www.waters.com/webassets/cms/library/docs/720004072en.pdf.
9. Karmarkar S, Garber R, Genchanok Y, George S, Yang X, Hammond R. Journal of Chromatographic Science, 2011; 49: 439-46.
10. Increased Process Understanding for QbD by Introducing Universal Detection at Several Stages of the Pharmaceutical Process, Dionex Corporation. www.dionex.com/en-us/webdocs/85934-pc-HPLC-CAD-process-QbD-March2010.pdf.
11. Gupta A, Fuloria NK. International Journal of Drug Development & Research, 2012; 4(3):19-26.
12. Nwoko VE. Journal of Global Trends in Pharmaceutical Sciences, 2013;4(4):1257-62.
13. EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel assessment, European Medicines Agency, www.ema.europa.eu and www.fda.gov
14. Understanding Challenge to Quality by Design, Food and Drug Administration, www.fda.gov.
15. Quality by Design and new ICH guidelines, Dr. Buket A.www.crsic.org/pdf/bucket-abstract.pdf.
16. Quality by Design, Vince McCurdy.2010; 30(4):12-32.
17. Using QbD for process optimization of a novel oral solid dosage form, Metrics. www.metricsine.com/up co ntent/upload/2012/10/50e-cobb-2012.pdf.
18. Integrating Quality by Design in medical device manufacturing, Stevens Institute of Technology. www.mdtmag.com/sites/white-paper/2010/07white-peper.
19. EMA-FDA pilot program for parallel assessment of Quality by Design applications, European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004147.pdf.
20. Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms, Food and Drug Administration. www.GenericDrugs@fda.hhs.gov.