WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 2420-2434. Review Article ISSN 2277– 7105

QUALITY BY DESIGN: A MODERN APPROACH TO PHARMACEUTICAL QUALITY

Ashwini Rajeshwar Adepu* **and Vijaya Bhogale**

Department of Quality Assurance, Dr. L. H. Hiranandani College of Pharmacy, University of Mumbai, Ulhasnagar.

Article Received on
16 March 2015,

Revised on 07 April 2015,
Accepted on 01 May 2015

***Correspondence for Author**
Ashwini Rajeshwar Adepu
Department of Quality Assurance, Dr. L. H. Hiranandani College of Pharmacy, University of Mumbai, Ulhasnagar.

ABSTRACT

Quality by Design is the modern approach for quality of pharmaceuticals. This paper gives idea about the Pharmaceutical Quality by Design (QbD) and describes use of Quality by Design to ensure quality of Pharmaceuticals. QbD has become the answer to assist both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development. The concept promotes industry's understanding of the product and manufacturing process starting with product development, basically building quality in, not testing it. It includes the Quality target product profile, critical quality attributes and key aspects of Quality by Design. It also gives comparison between product quality by end product testing and product quality by Quality by Design. The foundation of Quality by Design is ICH Guidelines. It is based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals.

KEYWORDS: Target Product Profile (TPP), Target Product Quality Profile (TPQP), Critical Quality Attributes (CQA), Critical Material Attributes (CMA), Critical Process Parameter (CPP), Design Space.

INTRODUCTION

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.[1] 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 information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space.[1] QbD requires an understanding of how product and process variables influence product quality. In addition to this new concept being considered by FDA in its cGMP initiative, two important guidance documents were published as part of International Conference on Harmonization (ICH) guidelines: Q8 Pharmaceutical Development and Q9 Quality Risk Management. Q10 Pharmaceutical Quality System also describes model for an effective quality management system for pharmaceutical industry. In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product.

Design

- Product is designed to meet patient needs and performance requirements.
- Process is designed to consistently meet product quality attributes.
- Impact of starting raw materials and process parameters on product quality is understood.
- Critical sources of process variability are identified and controlled.
- The process is continually monitored and updated to allow for consistent quality over time.

Definition [ICH Q 8(R1)]

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.[4]

Definition [FDA PAT Guidelines, Sept. 2004]

A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and processes, with the goal of ensuring final product safety.[5]

The application of QbD principles to pharmaceutical development and manufacturing has gained a lot of interest in the literature recently. The article describes a systematic and general scheme to implement QbD in the pharmaceutical industry and also illustrate key aspect of QbD process in the pharmaceuticals. Guidelines and mathematical models are used to ensure the establishment and use of the knowledge on the subject in an independent and integrated way.

Benefits of QBD[1,3,6,7]

- QbD is good Business
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Organizational learning is an investment in the future
- QbD is good Science
- Better development decisions
- Empowerment of technical staff.

Opportunities[1,7]

- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management.

Knowledge of product and process management and quality risk management are two of the primary components 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 continual improvement. Some knowledge includes.

- 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.[8-9]**OLVE**

A good understanding of the documentation relating to prior knowledge referenced in risk assessments and DoEs is a must for the success of Qbd.

Basic considerations of QbD

As far as pharmaceutical industry is considered safety of patient and providing a quality product have been given prime importance; and to achieve this target QbD assist it by thorough understanding of process which is the ultimate goal of QbD.

Advantages of QbD can be summarized as

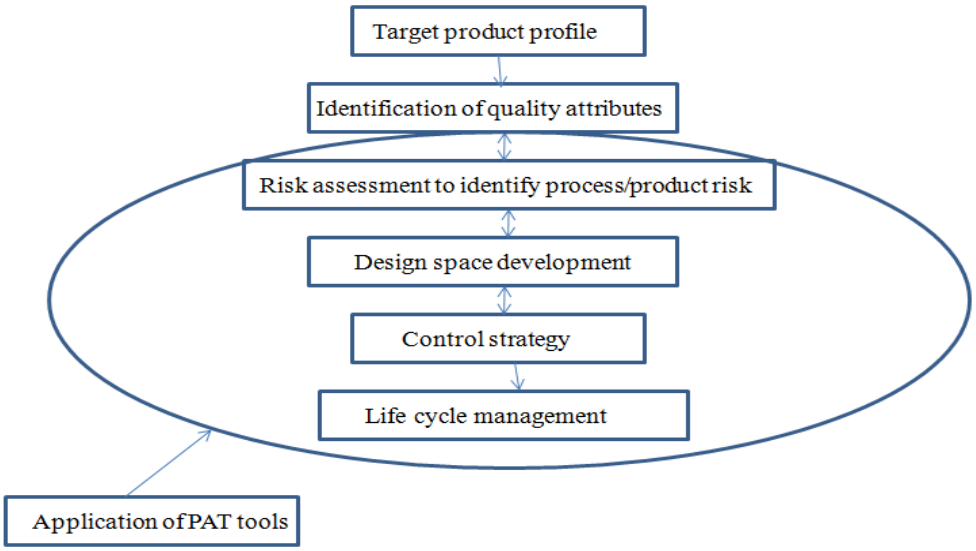
1. Patient safety and product efficacy are focused.
2. Scientific understanding of pharmaceutical process and methods is done.
3. It involves product design and process development.
4. Science based risk assessment is carried.
5. Critical quality attributes are identified and their effect on final quality of product is analysed.
6. It offers robust method or process.
7. Business benefits are also driving force to adopt QbD.

ELEMENTS OF QUALITY BY DESIGN

QbD comprises all elements of pharmaceutical development mentioned in the ICH guideline Q8. Pharmaceutical Development section is projected to provide a complete understanding of the product and manufacturing process for reviewers and inspectors. To design a quality product and its manufacturing process to consistently deliver the intended performance of product is the aim of pharmaceutical development. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the specifications, and manufacturing controls (Patricia, 2007).

Different elements of pharmaceutical development include,

1. Defining an objective
2. Determination of critical quality attributes (CQA)
3. Risk assessment
4. Development of experimental design
5. Designing and implementing control strategy
6. Continuous improvement.



1. IDENTIFYING TARGET PRODUCT QUALITY PROFILE (TPQP)

The quality target product profile (QTPP) as defined in ICH Q8(R1) 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.1This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and Excipients meeting specification Unit operation with fixed process parameters In process specification Finished product Specification Product meeting quality If fails, materials discarded If fails, product discarded aerodynamic performance) appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g., sterility and purity) appropriate for the intended marketed product. The FDA has published a guidance defining the Target Product Profile (TPP), that focuses on the consumer (patient) and the desired product label.[8-9] The Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly

deliver the therapeutic benefit promised in the label. The TPQP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label.[10-11]

TPP can play a central role in the entire drug discovery and development process such as

1. Effective optimization of a drug candidate is possible
2. Decision-making within an organization can be done.
3. Design of clinical research strategies, and
4.Constructive communication with regulatory authorities is easy.

Definition of TPP

"The TPP provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. Usually, the TPP is organized according to the key sections in the drug labeling and links drug development activities to specific concepts intended for inclusion in the drug labeling." When ICH Q8 says that pharmaceutical development should include "...identification of those attributes mthat 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 labeling centered 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 depended on the particular implementation and may differ between a generic and reference product.

2. Identification of 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.[3] Identification of CQAs is done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk

assessments. Such knowledge may also include relevant data from similar molecules and data from literature references. Taken together, this information provides a rationale for relating the CQA to product safety and efficacy.[10-11] The use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm. As shown in Fig.2, it seems more precise to consider the TPP, TPQP, 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.[14]

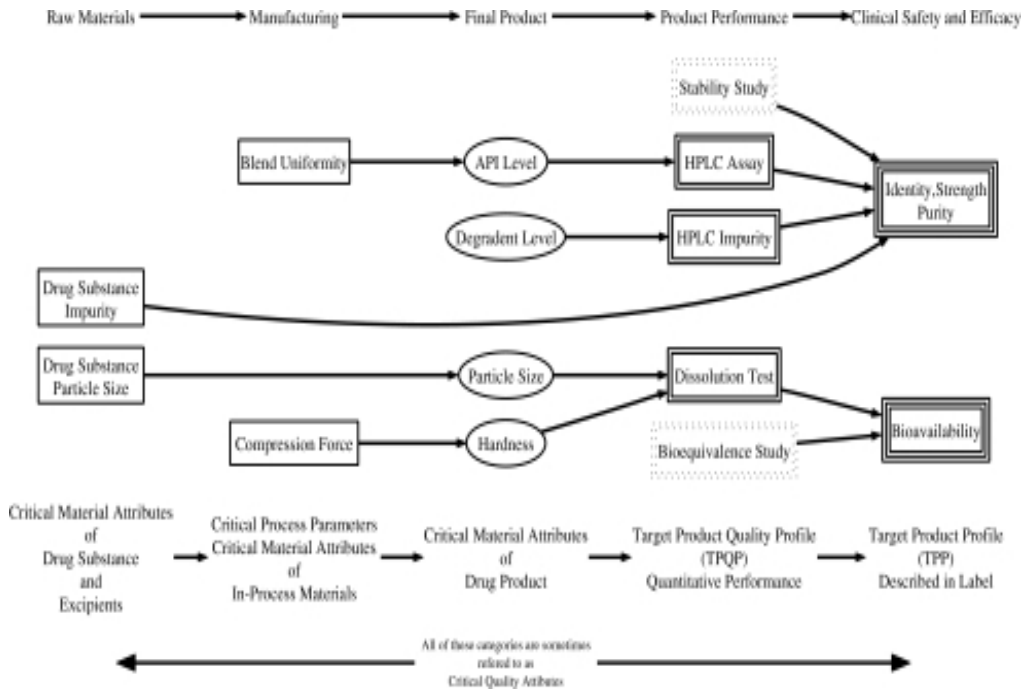


Fig.2. An Illustration of How Under QbD the Identification of Critical Process Parameters and Critical Material Attributes is Linked to the TPQP and Finally to TPP that Represents the Clinical Safety And Efficacy.

2.1.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.

2.2.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. 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.[8-9] 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.[14]

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.[14]

2.3.What is an Unclassified Process Parameter(UPP)?

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.

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

The criticality of an unclassified parameter is undetermined or unknown.[8-9]

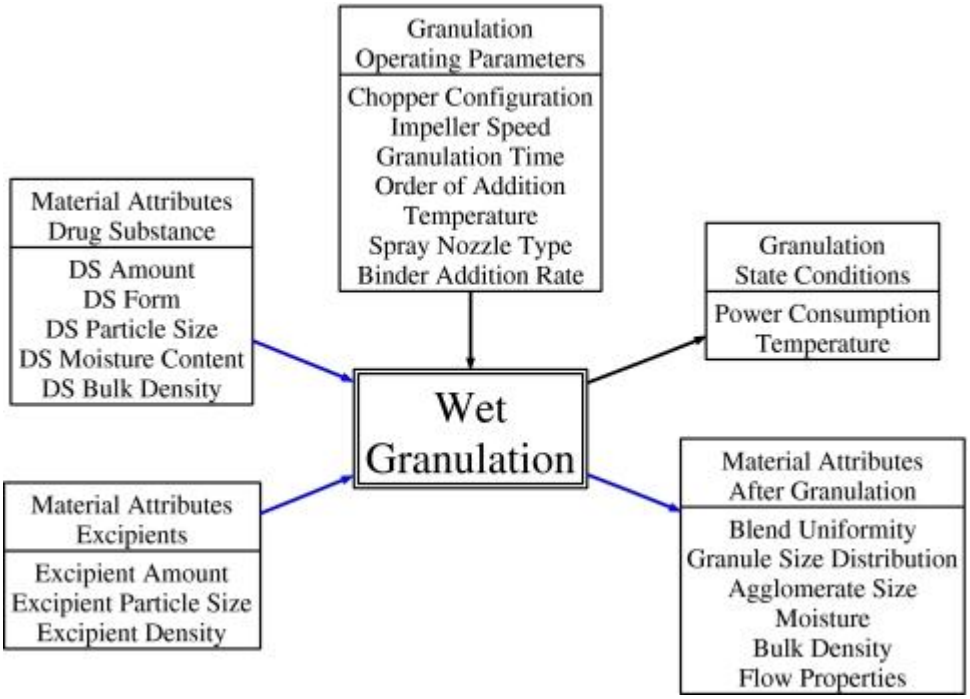


Fig.3.An Example of Identification of Process Parameters and Material Attributes Prior to Pharmaceutical Development

Figure 3 provides an example identification of unclassified process parameters (UPP) at the beginning of a development process. These UPP may later be classified as critical or noncritical. 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.[14]

2.4.What is a Critical Process Parameter (CPP)?

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. 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. 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.[8-9] 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 noncritical, 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.[8-9]

3. Quality Risk Assessment

The core of QbD is quality risk management (QRM). This is a systematic and integrated approach for assessment, control, communication and review of risks to the quality of the drug (medicinal) product and the associated manufacturing process across the product lifecycle. A key component of QRM is Quality Risk Assessment (QRA) which is an active tool to identify potential risks related to materials, processes, and/or handling. Subsequent mitigation then comprises adjusting designs and/or changing controls. Notably, QRA is not a single „tick-box" activity. Rather it is an active component of QRM throughout the product and process lifecycle. 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. Typical tools used include risk ranking and filtering, input–process–output diagrams, Ishikawa diagram, and so on. Several other tools are also available that help to prioritize the attributes/variables. 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.[8-9]

4.DESIGN PRODUCT AND DEFINING PRODUCT DESIGN SPACE: The **d**efinition of design space is "The multidimensional combination and interaction of input variables (eg. material attributes) and process parameters that has been demonstrated to provide assurance of quality ". The definition evolve 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 of multidimensional interaction of input variables and closely binds the establishment of design space to conduct of DOE that includes interactions among the input variables.5 It is the region where acceptable product can be produced. The normal operating range is a subset of the Design Space where routine manufacture is typically performed on a daily basis. Finally, the Control Strategy ensures that operation of the process is maintained within the Design Space. It is intended to prevent operating in regions of limited process knowledge or that are known to cause product failure.

The key advantages of using DOE approach are summarized as following

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

In a typical design space approach a sponsor identifies the unclassified parameters and then does a DOE on some of the unclassified parameters with the other unclassified parameters fixed. Thus the end is a regulatory situation where there is some space for the selected

parameters but no flexibility for the other parameters. This operating parameter based design space is limited to the equipment used to develop the design space. It might change on scale up or equipment changes.

In the development of a design space, the key issue to efficiency is demonstrating or establishing that the unclassified parameters left out of the DOE are truly non-critical process parameters and are thus by our definition non- interacting. Before attempting to establish a design space, effort should be invested to reduce the number of unclassified process parameters. This may involve a screening DOE to rule out significant interactions between process parameters. When they are non-interacting, univariate ranges for noncritical parameters are appropriate and can be added to the design space presentation without additional studies. It is best to exploit the non-uniqueness of CPPs to define the design space in terms of scale independent (dimensionless) parameters and material attributes. Understanding the design space in terms of material attributes allows scale up and equipment changes to be linked to previous experiments. The scalability of the design space can be evaluated in the transfer from lab to exhibit batch manufacturing.

5. CONTROL STRATEGY

Control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality". The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements: procedural controls, in-process controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach.[4]

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. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness. Manufacturer are also not permitted to make changes to the operating parameters (a large number of UPPs) specified in the batch record or other process changes without filling supplements with the FDA.[8]

Every process has a control strategy right now. Figure 4 shows a simplified quality assurance diagram under the current regulatory evaluation system. In this system, product quality is ensured by fixing the process to produce the active ingredient, raw material testing, performing the drug product manufacturing process as described in a fixed batch record, in-process material testing, and end product testing. The quality of raw materials including drug substance and excipients is monitored by testing. If they meet specifications or other standards such as USP for drug substance or excipients, they can be used for manufacturing of the products. As the drug substance specification alone may not be sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. Potentially significant changes to the drug substance manufacturing process will require the drug product manufacturer to file supplements with the FDA. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness. Manufacturer are also not permitted to make changes to the operating parameters (a large number of UPPs) specified in the batch record or other process changes without filling supplements with the FDA. This combination of fixed (and thus inflexible) manufacturing steps and extensive testing is what ensures quality.[14]

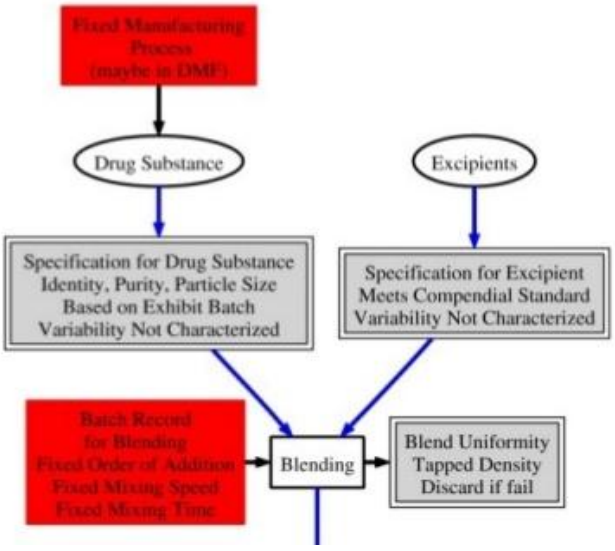


Fig. 4. An Example of Control Strategy for Pre-QbD Process

A QbD based control strategy is shown in Fig.5. Pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables to assure the quality of the finished product. The end product testing only confirms the quality of the product. The ranges of critical parameters must be constrained to a multidimensional design space or fixed

at values of all parameters known to be acceptable. Univariate PAR can be used for critical parameters only when there is evidence that there are no significant interactions between the CPP. However the establishment of this knowledge about CPPs may render them lower risk than UPP. A control strategy appropriate to the known CPP may also have less need for release testing than one for a process with many UPPs.[14]

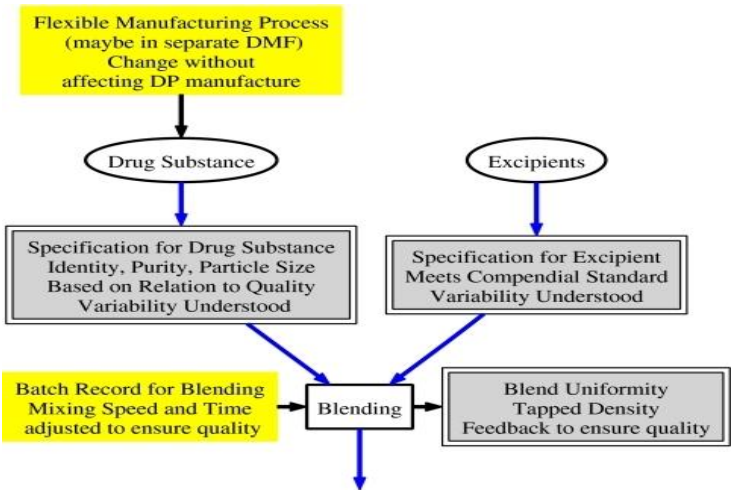


Fig.5. An Example of Control Strategy for QbD Process

6. CONCLUSIONS

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.

REFERENCE

1. Woodcock J, The concept of pharmaceutical quality. American Pharmaceutical Review, 2004; 7(6): 10–15.
2. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.

3. Q10: Pharmaceutical Quality System, ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.
4. Q8 (R1): Pharmaceutical Development, Revision 1, ICH Harmonized Tripartite Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.
5. FDA Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool (Draft Guidance).
6. Callis JB, Illman DL, Kowalski BR, Process analytical chemistry. Analytical Chemistry, 1987; 59: 624A–637A.
7. Yu LX, Pharmaceutical quality by design: Product and process development, understanding, and control. Pharmaceutical Research, 2008; 25: 781–791.
8. Gupta Anuj* and Dr Neeraj Kumar Fuloria "Short review on Quality by design: A new Era of Pharmaceutical drug development", Int. J. Drug Dev.& Res., July-September 2012; 4(3): 19-26.
9. FDA CDER. Draft guidance for industry and review staff. Target product profile-strategic development process tool, March 2007.
10. Food and Drug Administration Office of Generic Drugs. *Model Quality Overall Summary for IR Product*, http:// www.fda.gov/ cder/ ogd/OGD_Model-QoS_IR_Product.pdf (Accessed March 31, 2006).
11. Sandipan Roy, Quality by design: A holistic concept of building quality in pharmaceuticals. *Int J Pharm Biomed Res.,* 2012; *3*(2): 100-108.
12. US Food and Drug Administration, *Pharmaceutical cGMPs for the 21st century: A Risk Based Approach*, FDA, Rockville, MD, August 2002.
13. Food and Drug Administration CDER. Guidance for industry:Changes to an approved NDA or ANDA, 2004.
14. The AAPS Journal, Vol. 10, No. 2, June 2008 (# 2008)DOI: 10.1208/s12248-008-9026-7 Quality by Design: Concepts for ANDAs Robert A. Lionberger,1 Sau Lawrence Lee,1 LaiMing Lee,1 Andre Raw,1 and Lawrence X. Yu1,2 Received 7 December 2007; accepted., 29 February 2008.