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A Review on Quality by Design Approach (QBD) for Pharmaceuticals

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ABSTRACT

Quality by Design is the modern approach for quality of pharmaceuticals. It describes use of Quality by Design to ensure quality of Pharmaceuticals. In this review, the Quality by Design is described and some of its elements identified. Process parameters and quality attributes are identified for each unit operation. Benefits, opportunities and steps involved in Quality by Design of Pharmaceutical products are described. 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. 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.

Keywords: QbD design, ICH, QTPP, CQA, PAT.

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INTRODUCTION

Quality means fitness for intended use. Pharmaceutical quality refers to product free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests. Quality by design assures in vitro product performance and In vitro product performance provides assurance of in vivo product performance. “Hence Quality by design relate to Product Performance”. (1)

Quality by Design (QbD) is a modern, scientific approach that formalizes product design, automates manual testing, and streamlines troubleshooting. It uses a systematic approach to ensure quality by developing a thorough understanding of the compatibility of a finished product to all of the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insights upstream throughout the development process. As a result, a quality issue can be efficiently analyzed and its root cause quickly identified.

QbD requires identification of all critical formulation attributes and process parameters as well as determining the extent to which any variation can impact the quality of the finished product. The more information generated on the impact – or lack of impact – of a component or process on a product’s quality, safety or efficacy, the more business flexibility Quality by Design provides.

While medicine is well known as special goods, the development of pharmaceutical industry is based on innovation and manufacturing. However, there are lots of complaints from pharmaceutical industry about the strict rules. In current quality by test (QbT) system, product quality is ensured by following a sequence of steps, including raw material testing, fixed drug product manufacturing process, and end product testing. It is only when all the specifications of the FDA or other standards are complied with that the materials can be used for manufacturing or come into market. If not, they need to be reprocessed. Root causes for failure are usually not well understood due to the poor process understanding and uncertainty about how characteristics of substances impacts target product profile. As a result, the manufacturers have to restart the procedure until the root causes of failure are understood and addressed or FDA approves supplements to revise (e.g., widen) the acceptance criteria to pass the previously failed batches. This causes poor cost-efficiency and product variation, which may lead to poor drug safety.

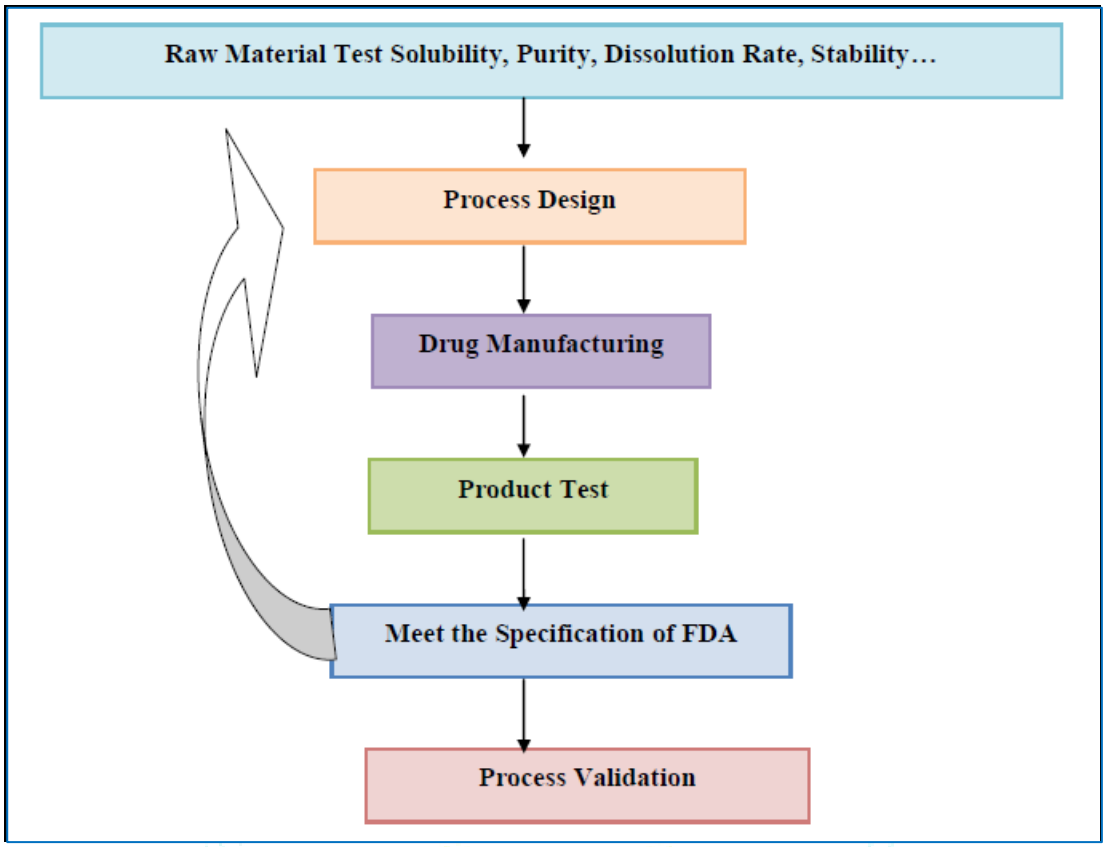

Figure. 1 Quality by Thought (QbT)

Definition

The 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. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance.(2)

Objectives of QbD:

- The main objectives of QbD is to ensure the quality products, for that product & process characteristics important to desired performance must be resulting from a combination of prior knowledge & new estimation during development.
- From this knowledge & data process measurement & desired attributes may be constructed.
- Experimental study would be viewed as positive performance testing of the model ability through Design space.
- Ensures combination of product & process knowledge gained during development.

QbD BY PHARMACEUTICALS (3)

Even though the pharmaceutical industry has focus on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity.

Current scenario in the Pharmaceutical Industry:

- Cost of revalidation
- Off-line analysis for in-process - need based
- Product specifications as primary means of control
- Unpredictable Scale-up issues
- Inability to understand failures

Systematic approach to development:

- That begins with predefined objectives
- Emphasizes products and process understanding
- Process control

Benefits of QbD

- 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

- 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

For industry:

- Better understanding of the process.
- More efficient and effective control of change.
- Return on investment / cost savings
- Less Batch failure.
- Ensure better design of products with less problems in manufacturing.
- Allows for continuous improvement in products & manufacturing process

For FDA:

- Enhances scientific base for analysis.
- Provide better consistency.
- Provide for more flexibility in decision making.
- Ensures decisions made on science & not on observed information.

STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS

- **Development of new molecular entity**
- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval
- **Manufacturing**
- Design Space
- Process Analytical Technology
- Real time Quality Control
- **Control Strategy**
- Risk based decision
- Continuous Improvement
- Product performance

Seven steps of quality by design start up plan

- Hire an independent Quality by design expert.
- Audit your organization and process with the expert conducting a gape analysis.
- Hold a basic quality by design workshop with all your personal.
- Review the expert's report and recommendation.
- Draft an implementation plan, timelines and estimated costs.
- Assign the resources (or contract out).
- Retain the independent expert as your "Project Assurance" advisor.

Quality by design (QbD) and well understood product and processes

- All critical sources of variability are identified and explained.
- Variability is controlled by the process.
- Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions.
- To gain enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters considering appropriate use of quality risk management principles.

QbD development process include :(4,5)

- 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 input (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 input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass 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. They are not check-box requirements.

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD (Figure:2)

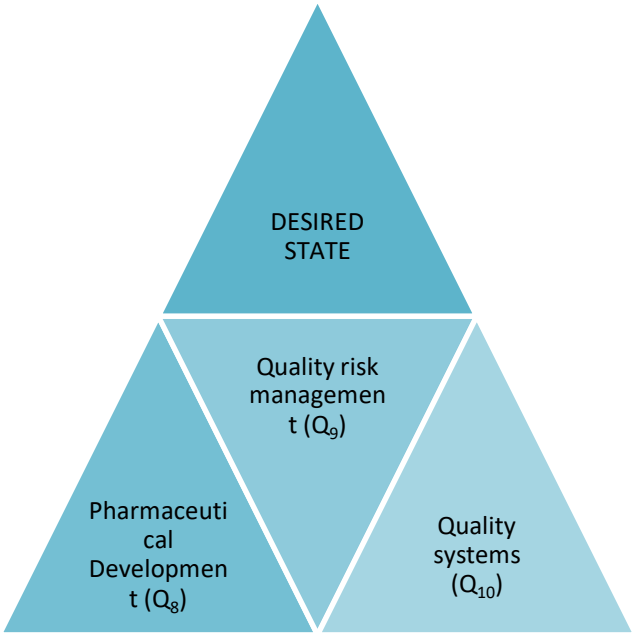

Figure 2. ICH guidelines of QbD

Quality by Design (6,7,8,9)

- Concepts aligned
- Design Space - Key to understanding
- Process robustness
- Design of Experiments (DOE)
- Quality management Quality management

Advantages of QbD

• It provides a higher level of assurance of drug product quality.

• It offers cost savings and efficiency for the pharmaceutical industry.

• It increases the transparency of the sponsor understands the control strategy for the drug product to obtain approval and ultimately commercialize.

• It makes the scale-up, validation and commercialization transparent, rational and predictable.

• It facilitates innovation for unmet medical needs.

• It increases efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.

• It minimizes or eliminates potential compliance actions, costly penalties, and drug recalls.

• It offers opportunities for continual improvement.

• It provides more efficiency for regulatory oversight:

• It streamlines post approval manufacturing changes and regulatory processes.

• It more focused post approval CGMP inspections

• It enhances opportunities for first cycle approval.

• It facilitates continuous improvement and reduces the CMC supplement.

• It enhances the quality of CMC and reduces the CMC review time.

Benefits for Industry:(10)

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.

Additional opportunities:

An enhance QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches.

Ex: Manufacturing changes within the approved design space without further regulatory review.

- Reduction of post-approval submissions.
- Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.
- More efficient technology transfer to manufacturing.
- Greater regulator confidence of robust products.
- Risk-based approach and identification.
- Innovative process validation approaches.
- Less intense regulatory oversight and less post-approval submissions.
- For the consumer, greater drug consistency.
- More drug availability and less recall.
- Improved yields, lower cost, less investigations, reduced testing, etc.
- Time to market reductions: from 12 to 6 years realized by amongst others.
- First time right: lean assets management.
- Continuous improvement over the total product life cycle (i.e. controlled, patient guided variability).
- Absence of design freeze (no variation issues).
- Less validation burden.
- Real time controls (less batch controls).
- Realistic risk perceptions.
- Contributes substantially to realize the better, cheaper and safer mandate.

QbD activities within FDA(11,12,13,14)

Specifically, the following activities are guiding the overall implementation of QbD:

- In FDA's Office of New Drug Quality Assessment (ONDQA), a new risk-based pharmaceutical quality assessment system (PQAS) was established based on the application of product and process understanding.
- Implementation of a pilot program to allow manufacturers in the pharmaceutical industry to submit information for a new drug application demonstrating use of QbD principles, product knowledge, and process understanding. In 2006, Merck & Co.'s Januvia became the first product approved based upon such an application.
- Implementation of a Question-based Review (QbR) Process has occurred in CDER's Office of Generic Drugs.

- CDER's Office of Compliance has played an active role in complementing the QbD initiative by optimizing pre-approval inspectional processes to evaluate commercial process feasibility and determining if a state of process control is maintained throughout the lifecycle, in accord with the ICH Q10 lifecycle Quality System.
- Implementation of QbD for a Biologic License Application (BLA) is progressing.

While QbD will provide better design predictions, there is also a strong recognition that industrial scale-up and commercial manufacturing experience provides new and very important knowledge about the process and the raw materials used therein. FDA is aware that knowledge is not static and builds throughout the manufacturing lifecycle.

FDA's release of the Process Validation guidance in January 2011 notes the need for companies to continue benefiting from knowledge gained, and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are quickly corrected. This vigilant and nimble approach is explained by FDA to be essential to best protect the consumer (patient).

International Conference on Harmonization. (ICH)(15-22)

Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (ICH)

- Pharmaceutical Development Q8 (R2)
- Quality Risk Management Q9
- Pharmaceutical Quality System Q10

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.

Quality by design (QbD) encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. The concept of quality by design (QbD) has been recently adopted in the pharmaceutical industry through several initiatives {e.g., ICH Q81, Q92and Q103, and the new regulatory documents, Process Analytical Technology (PAT)5, FDAs cGMP for the 21st Century4}. The general aim is to switch from the quality by testing (QbT) paradigm previously implemented in the pharmaceutical industry to a development aimed at improving the understanding of the processes and the products and hence improving product quality, process efficiency and regulatory flexibility.

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. 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. Information from pharmaceutical development studies can be a basis for quality risk management. 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. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful.

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process1. The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question based review (QbR) for its chemistry, manufacturing and controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs). QbR is a new quality attributes. It is a practical implementation of some underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the twenty first century and quality by design (QbD) initiatives6. Figure 1, which illustrates the different phases during the life cycle of a pharmaceutical process: define, design, characterize, validate, and monitor and control. The final link between "monitor and control" and "define" represents process changes that are initiated based on process improvement opportunities identified during process monitoring or introduced otherwise to improve process performance or robustness. Changes originating in this manner would again go through the cycle illustrated in Fig.3

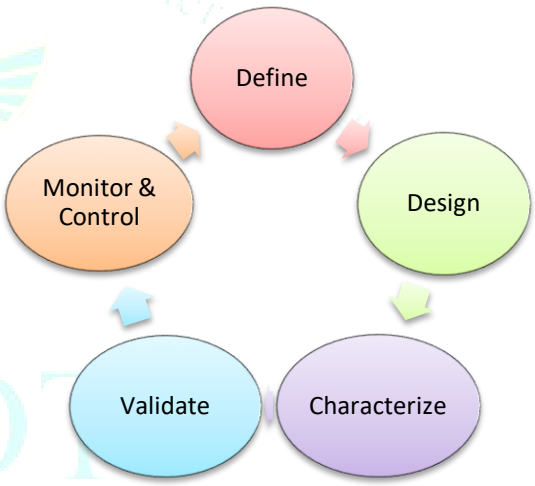

Fig 3: Illustration of the different steps in development of a pharmaceutical product. Pharmaceutical Quality by Design

Pharmaceutical Quality by Design ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. "ICH Q8 guideline states that Quality by Design 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 Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD (Fig. 2) "Product testing alone is not sufficient to assure that a process consistently produces a product with predetermined specifications. Adequate process design; knowledge and control of factors that produce process variability and successful validation studies, in conjunction with product testing, provide assurance that the process will produce a product with the required quality characteristics".

Table 1: Difference between current approach and Qbd approach

Current Approach	QbD Approach
Quality is assured by testing and inspection.	Quality is built into product & process by design and based on scientific understanding.
It includes only data intensive submission which includes disjointed information without "big picture".	It includes Knowledge rich submission which shows product knowledge & process understanding.
Here, any specifications are based on batch history.	Here, any specifications based on product performance requirements.
Here there is "Frozen process," which always discourages changes.	Here there is Flexible process within design space which allows continuous improvement.
It focuses on reproducibility which often avoids or ignores variation.	It focuses on robustness which understanding & control variation.

There are several statements about the elements of QbD, the most widely accepted is that, QbD consists of the following parameters.

ELEMENTS OF QbD :(23-29)

1) Quality Target Product Profile (QTPP):

It including dosage form, delivery systems, dosage strength(s), etc. It is a prospective summary of quality characteristics of a drug product to be achieved, taking into account dosage strength(s) and container closure system of the drug product, together with the attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) and drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

QTPP has been defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized". This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and 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 role of target product profile (TPP) is to serve as a tool for "quality planning" for the drug product with "the end in mind" i.e. a summary of the drug development program described in the context of prescribing information goals. A quality target product profile (QTPP) is a term which is a natural extension of TPP for product quality .A QTPP relates to the quality of a drug substance or the drugs products that is necessary to deliver a desired therapeutic effect .QTPP is a predetermined summary of the characteristics of the drug product that will ideally be essential to ensure the desired quality with respect to safety and efficacy of the product. These predetermined QTPP evolve over time during drug development and may be modified to incorporate new knowledge, as is warranted by ongoing clinical studies such a dose effect and toxicology data.

The 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 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. Biopharmaceutical properties of drug substance include physical, chemical, and biological properties. 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 concept of TPP in this form and its application is novel in the QbD paradigm. TPP forms the basis for product design in the following way.

- Dosage form
- Route of administration
- Strength, maximum and minimum
- Release/delivery of the drug Pharmacological characteristic
- Drug product quality criteria
- Pharmaceutical elegance

Critical Quality Attribute (CQA):

It including physical, chemical, biological, or microbiological properties or characteristics of an output material including finished drug product. Potential drug product CQAs derived from the QTPP and/or prior knowledge are used to guide the product and process development and they should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Once TPP has been identified, the next step is to identify the relevant CQAs. A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distributed to ensure the desired product quality" 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. This information provides a rationale for relating the CQA to product safety and efficacy. The use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm.Critical quality attributes are defined as physical, chemical, biological or microbiological properties or characteristics that need to be controlled to ensure product quality.(According to ICH Q8) 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. CQA has been used by some to

describe elements of the TPQP while others have used CQA to describe mechanistic factors that determine product performance. Thus CQA is used to describe both aspects of product performance and determinants of product performance.

Once TPQP has been identified, the next step is to identify the relevant CQAs. A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distributed to ensure the desired product quality" 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.

This information provides a rationale for relating the CQA to product safety and efficacy. The use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parentral , and adhesion properties for transdermal patches . For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs.

3) Critical Material Attributes (CMAs):

including physical, chemical, biological, or microbiological properties or characteristics of an input material. CMAs should be within an appropriate limit, range, or distribution to ensure the desired quality of that drug substance, excipient, or in-process material.

4) **Critical Process Parameters (CPPs):**

Parameters monitored before or in process that influence the appearance, impurity, and yield of final product significantly.During the QbD process, product design and understanding include the identification of CMAs, which are different from CQAs. CQAs are for output materials while CMAs are for input materials including drug substance, excipients, in-process materials. The CQA of an intermediate may become a CMA of the same intermediate for a downstream manufacturing step. While process design and understanding include the identification of CPPs and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs is of special importance. From the viewpoint of QbD, CMAs and CPPs can vary within the established Design Space without significant influence on CQAs, and as a result, the quality of the final product will meet the QTPP.

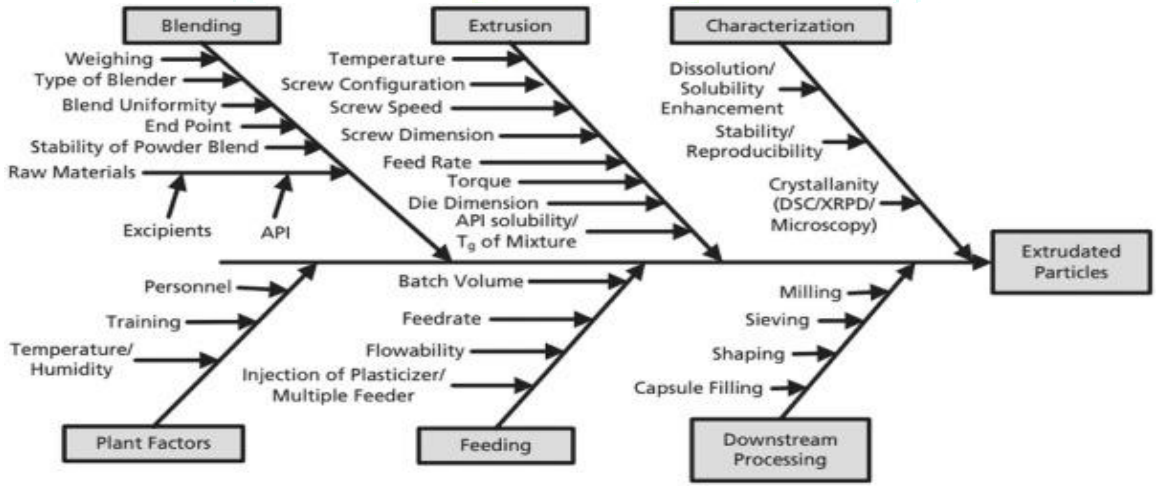

Figure 4.

5) Risk assessment

Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. It is the first step of quality risk management process; the other two steps are risk control and risk review. Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. At the final stage, the output/results of the risk management process should be reviewed to take into account new knowledge and experience. Throughout the risk management process, risk communication, the sharing of information about risk and risk management between the parties (including regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc.), should be ongoing at any stage of the risk management process. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality .

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.

It is nothing but linking material attributes and process parameters to CQAs. ICH Q9 Quality Risk Management indicates that, the manufacturing and use of a drug product necessarily lead to some degree of risk. The evaluation of the risk of quality should be based on scientific knowledge and link to the therapeutic benefit to the patient. The level of effort, formality and documentation of the quality risk management process should be proportionate with the level of risk. Performing a risk assessment before pharmaceutical development helps manufacturers decide which studies to conduct. Study results determine which variables are critical and which are not, which then guide the establishment of control strategies for in-process, raw-material, and final testing.

Several applications in the CMC pilot included risk assessments, especially for the drug product by linking input and process variables to CQAs. Tools used in the risk assessment included the Ishikawa or Fishbone diagram, failure mode effect analysis (FMEA), Pareto analysis. An Ishikawa or Fishbone diagram is used to identify all potential variables, such as raw materials, compression parameters, and environmental factors, which can have an impact on a particular CQA such as tablets hardness. An FMEA can be used to rank the variables based on risk (i.e., a combination of probability, severity, and detectability) and to select the process parameter with higher risks for further studies to gain greater understanding of their effects ion CQAs

There are three components of risk assessment, that is, risk identification, risk analysis and risk evaluation.

(1) Risk Identification: The systematic use of information to identify potential sources of harm (hazards) that are referring to the risk question or problem description, which can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders;

(2) Risk Analysis: The estimation of the risk associated with the identified hazards;

(3) Risk Evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

ICH Q9 provides a non-exhaustive list of 9 common risk management tools as follows:

(1) Basic risk management facilitation methods (Ishikawa fishbone diagram, flowcharts, check sheets, etc.);

(2) Fault tree analysis;

(3) Risk ranking and filtering;

(4) Preliminary hazard analysis;

(5) Hazard analysis and critical control points;

(6) Failure mode and effects analysis (FMEA);

(7) Failure mode, effects, and criticality analysis (FMECA);

(8) Hazard operability analysis;

(9) Supporting statistical tools.

According to the implementation of QbD, risk assessment has the priority over DoE. Among the tools, Ishikawa fishbone diagram and FMEA are widely used approaches for risk assessment, either separately or in combination . Taking the preparation of extruded particles as an example, the Ishikawa diagram is shown in . The risk factors in the fishbone diagram are classified into broad categories, while the FMEA could identify the failure modes that have the greatest chance of causing product failure, which means each of the factors in the Ishikawa fishbone diagrams will be ranked later in the FMEA analysis. The FMEA method can be used to perform the quantitative risk assessment, identifying the CQAs that have the greatest chance of causing product failure. The outcome of an FMEA are risk priority numbers (RPN) for each combination of failure mode severity, occurrence probability, and likelihood of detection.

6) Design of experiment (DoE)

To carry out the design of experiment, the risk assessment should be taken into function first. A structured, organized method for determining the relationship between factors affecting a process and the output of that process is known as “Design of Experiments” (DoE). DoE is an excellent tool that allows pharmaceutical scientists to systematically manipulate factors according to a pre-specified design. A good design is based on sound cognition of product and effective management of whole process during manufacturing. DoE studies work together with mechanism-based studies to achieve better product and process understanding.

DoE is a reasonable method to determine the relationship between the inputs and outputs of a process. It can help identify optimal conditions, CMAs, CPPs, and, ultimately, the Design Space. It is wise to establish a Design Space through DoE for multivariate experiments. ICH Q8 defines the 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” . It has been reported that there is no need to hand over supplements to revise (e.g., widen) the acceptance criteria to FDA if the changes are within the Design Space. Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. It has been suggested that DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. A methodology for designing experiments was proposed by Ronald A. Fisher, in his innovative book.The Design of Experiments (1935). Application of DOE in QbD helps in gaining maximum information from a minimum number of experiments. When DOE is applied to a 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 the 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 who do not, as well as details such as the existence of interactions and synergies between factors . One Factor at a time and Design of experiments.

So far, a number of studies have been launched in the drug delivery systems after QbD initiative was claimed, as summarized in . It has been demonstrated that DoE is effective in the design of different dosage forms and unit operations, it can be used more broadly in the near future to guarantee high research efficiency with improved product quality.

7) Design-space

ICH Q8 defines design space as, the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality. Moving out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. The design space is proposed by the applicant and is subject to regulatory assessment and approval. Design space is potentially scale and equipment dependent, the design space determined on the laboratory scale may not be relevant to the process at the commercial scale. Therefore, design-space verification at the commercial scale becomes essential unless it is confirmed that the design space is scale-independent. Currently, generic drug sponsors obtain information about acceptable ranges for individual CPPs and CMAs at laboratory or pilot scales.

Multidimensional combination of and interaction of input variables and process parameters that have been demonstrated to provide Quality Assurance.

ICH Q8 (R1) defines design space as, the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality. Moving out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. The design space is proposed by the applicant and is subject to regulatory assessment and approval. Design space is potentially scale and equipment dependent, the design space determined on the laboratory scale may not be relevant to the process at the commercial scale. Therefore, design-space verification at the commercial scale becomes essential unless it is confirmed that the design space is scale-independent. Currently, generic drug sponsors obtain information about acceptable ranges for individual CPPs and CMAs at laboratory or pilot scales.

Process Analytical Technology (PAT)-

PAT has been defined as "A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". The goal of PAT is to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." The design space is defined by the key and critical process parameters identified from process characterization studies and their acceptable ranges. These parameters are the primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and result in improved process robustness. NIR act as a tool for PAT and useful in the RTRT (Real Time Release Testing) as it monitors the particle size, blend uniformity, granulation, content uniformity, polymorphism , dissolution and monitoring the process online, at the line and offline, thus it reduces the release testing of the product

PAT as an important tool of QbD

PAT is defined as "Tools and systems that utilize real-time measurements, or rapid measurements during processing, of evolving quality and performance attributes of in-process materials to provide information to ensure optimal processing to produce final product that consistently conforms to established quality and performance standards".

ICH Q8 identifies the use of PAT to ensure that the process remains within an established Design Space.

The concept originates from the desire of the regulators to shift control of product quality toward a science-based approach that explicitly attempts to reduce the risk to patients by controlling the manufacturing based on understanding of the process.

PAT REGULATORY APPROACH

One goal of this guidance is to tailor the Agency's usual regulatory scrutiny to meet the needs of PAT-based innovations that

(1) Improve the scientific basis for establishing regulatory specifications,

(2) Promote continuous improvement, and

(3) Improve manufacturing while maintaining or improving the current level of product quality. To be able to do this, manufacturers should communicate relevant scientific knowledge to the Agency and resolve related technical issues in a timely manner. Our goal is to facilitate a consistent scientific regulatory assessment involving multiple Agency offices with varied responsibilities.

This guidance provides a broad perspective on our proposed PAT regulatory approach. Close communication between the manufacturer and the Agency's PAT review and inspection staff will be a key component in this approach. We anticipate that communication between manufacturers and the Agency may continue over the life cycle of a product and that communication will be in the form of meetings, telephone conferences, and written correspondence.

All marketing applications, amendments, or supplements to an application should be submitted to the appropriate CDER or CVM division in the usual manner. When consulting with the Agency, manufacturers may want to discuss not only specific PAT plans, but also thoughts on a possible regulatory path. Information generated from research on an existing process, along with other process knowledge, can be used to formulate and communicate implementation plans to Agency staff. In general, PAT implementation plans should be risk based. We are proposing the following possible implementation plans, where appropriate: PAT can be implemented under the facility's own quality system. CGMP inspections by the PAT Team or PAT certified Investigator can precede or follow PAT implementation.

Contains Nonbinding Recommendations A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT Team or PAT certified Investigator before implementation. A comparability protocol5 can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. Following approval of this comparability protocol by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation. To facilitate adoption or approval of a PAT process, manufacturers may request a preoperational review of a PAT manufacturing facility and process by the PAT Team (see ORA Field Management Directive No.135)6 by contacting the FDA Process Analytical Technology Team at the address given above. It should be noted that when certain PAT implementation plans neither affect the current process nor require a change in specifications, several options can be considered. Manufacturers should evaluate and discuss with the Agency the most appropriate option for their situation.

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