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Pharmaceutical Quality-by-Design (QbD): Basic Principles

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ABSTRACT

In this era of competition, quality is a prime factor of importance. The principles of quality have been described by the ICH guidelines: Q8 Pharmaceutical development, Q9 Pharmaceutical quality risk management and Q10 Pharmaceutical quality system. Quality-by-design is a recent concept which has been added as an annex to ICH Q8. It is a scientific approach that helps to build in quality into the product rather than mere testing of the final product. For the implementation of QbD various tools are needed to be used which have been described briefly. Risk assessment approaches, process analytical technology tools and mathematical, statistical and continuous improvement tools are important elements of quality by design, which mainly focus on the identification of critical parameters and defining a design space statistically. The basic principles of these three ICH guidelines with regard to quality of pharmaceutical products have been briefly discussed.

INTRODUCTION

In the 1990s, harmonisation around the world got going when the ICH proved to be effective in bridging many of the gaps that existed in almost all parts of the documentation required for new drug applications. The optimism fuelled by successful introduction of the first round of harmonized documentation helped to overcome the inertia that had so far beset the international scene. All the major objectives with regard to quality issues are being addressed by the ICH guidelines [1].

The three ICH guidelines which throw light upon quality-by-design and related aspects include Q8 Pharmaceutical development, Q9 Pharmaceutical risk management and Q10 Pharmaceutical Quality systems. In fact, the ICH guideline Q8 is sub-divided into two parts: part one deals with pharmaceutical development and Part II is the annex to the guideline which states the principles for Quality-by-Design (QbD) [2,3,4].

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.

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. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to understand a company's strategy better. Product and process understanding can be updated with the knowledge gained over the product lifecycle [2,5].

During early days, the quality of the product was measured by end product testing (commonly referred to as quality by testing). However, this would be inefficient. In July 2003, the experts from the three regional grouping (USA, EU, and Japan) working on the Quality Topics within ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) created a vision for the future pharmaceutical quality system. This vision recognizes that regulatory agencies will also benefit from this initiative as it will enable them to prioritize and allocate resources more efficiently, and in turn the patients too will be benefitted from improved access to medicines with enhanced assurance of quality [6].

Historical Background

In 2007, the FDA received a total of 5000 proposals for new drug applications (NDAs) and biological license applications and abbreviated new drug applications (ANDAs). 'Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach' was launched by the FDA in August 2002. A further guidance on process analytical technology (PAT) was released as part of the 'cGMPs for the 21st Century' initiative, which hoped to encourage the adoption of more modern and flexible manufacturing technology in the pharmaceutical industry [7,8].

In March 2004, the FDA launched The Critical Path Initiative (CPI) to address the steep decline in the number of innovative pharmaceutical products submitted for approval. The national strategy was to modernize the pharmaceutical sciences through which FDA-regulated products are developed, evaluated, manufactured and used [9].

This prompted to the publishing of a guideline to aid manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current thinking for cGMP regulations. The impetus is to have quality in-built. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization [10].

Good manufacturing practices for the 21st century have been continually evolving as the ICH quality initiatives have been adopted. The move from empirical assessment based on performance to the concept of "building quality in" based on critical attributes has gained

traction as new guidance documents have been published. The ICH published a series of guidance documents supporting QbD approaches that are highlighted in:

ICH Q8 Pharmaceutical Development – provides information on how to present knowledge gained when applying scientific approaches and quality risk management for developing and manufacturing a product. The annex ICH Q8 (R2) further clarifies the key concepts of QbD [10].

It is in the ICH Q8 annex that QbD is clearly defined as, "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". Two other important terms for discussing QbD were also defined in ICH Q8; Design Space and PAT. Design space is defined 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". According to ICH Q8, working within the design space is not considered as a change as it has been demonstrated to have no impact on quality. Movement out of the design space would be considered to be a change and would normally initiate a regulatory post-approval change process. Based on this guideline, design space was to be proposed by the applicant and would be subject to regulatory assessment and approval. PAT was also defined in ICH Q8 as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality" [11].

It should be emphasized that the ICH Q8 guideline provides guidance on the suggested contents of the Pharmaceutical Development section of the Common Technical Document. This section of regulatory submissions relates to the manufacturing of the 'drug product' which is a very specific term relating to the product that will actually be administered to the patient. This is in contrast to 'drug substance' or 'bulk material' which are the terms usually given to the active pharmaceutical ingredient (API) that is subsequently formulated with excipients to produce the drug product (formulation). This difference between drug product and drug substance is important when considering how and to what extent the original guidance was intended to apply QbD concepts and controls to pharmaceutical and biopharmaceutical manufacturing. This original guideline is not related to the manufacturing of 'drug substance' – the active

pharmaceutical ingredient (API) before it is formulated for administration to the patient. The complexity of unit operations for drug product is generally less than that for drug substance and it is appropriate that more control should be demonstrated for the drug product which will actually be administered to humans. The ICH Q8 guideline indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences could create a basis for flexible regulatory approaches. The guideline lays emphasis on more flexible regulatory approaches which could be achieved if the applicant could demonstrate an 'enhanced knowledge' of product performance over a range of material attributes, manufacturing process options and process parameters. The methods suggested to achieve this enhanced knowledge were formal experimental designs or Design of experiments (DoE) studies, PAT and prior knowledge. It was also recommended to use Quality Risk Management principles to carry out additional studies to acquire knowledge. ICH Q8 stresses that it is the level of knowledge gained and not the volume of data generated that would lead to more favourable consideration by the regulatory bodies. It was further suggested that applicant companies could assess the robustness of the manufacturing process, the ability of the process to reliably to produce a product of the intended quality. The guideline suggests that changes during development should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space [2,7].

Figure 1 illustrates an example of a risk-assessment tool. In this, a cross-functional team of experts work together to develop an Ishikawa (fish-bone) diagram that identifies potential variables which can have an impact on the desired quality attributes. Then, the variables are ranked on probability, severity, and detectability using FMEA analysis or similar tools. Design of experiments or other tools are then used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy. Given below, is a fish-bone diagram for the manufacturing of tablets [2].

Ishikawa Diagram

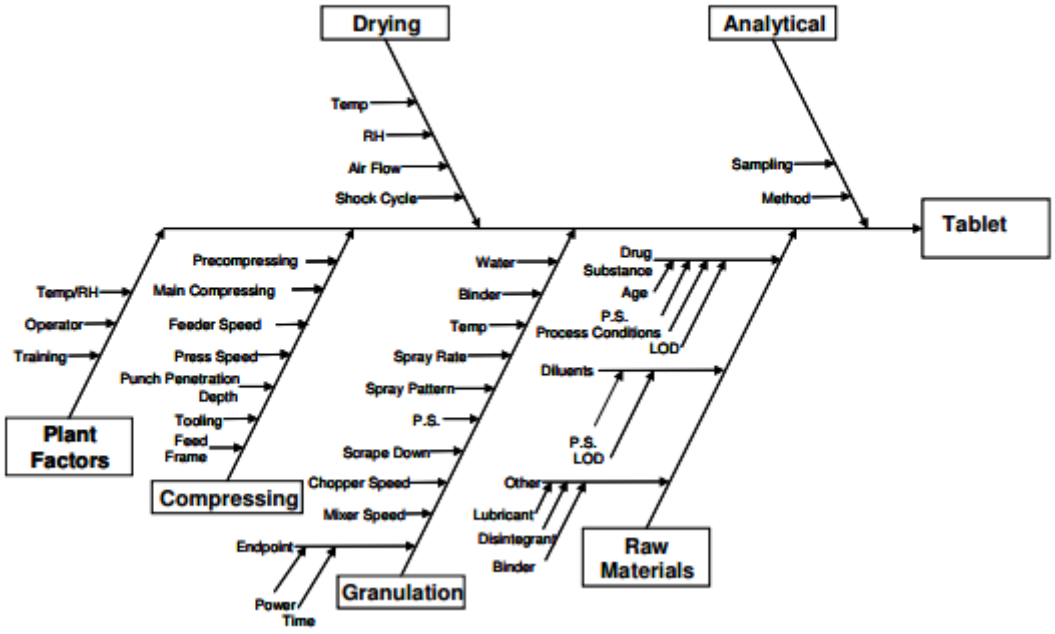

Figure 1: Fish-bone diagram for manufacturing of tablets

ICH Q9 Quality Risk Management – provides general guidance and references for some of the primary tools used in risk assessment. Examples are provided for industry and regulators to evaluate the risk to quality based on scientific knowledge and risk to patient [10].

This guideline was released at approximately the same time as ICH Q8 and ICH Q10, and needs to be considered as part of the overarching QbD guidance released by regulatory agencies. The purpose of ICH Q9 was to offer a systematic approach to quality risk management. Importantly, it is noted that use of quality risk management can "facilitate, but does not obviate, industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators". Two important principles were highlighted in this document for the use of Quality Risk Management:

1. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient;

2. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

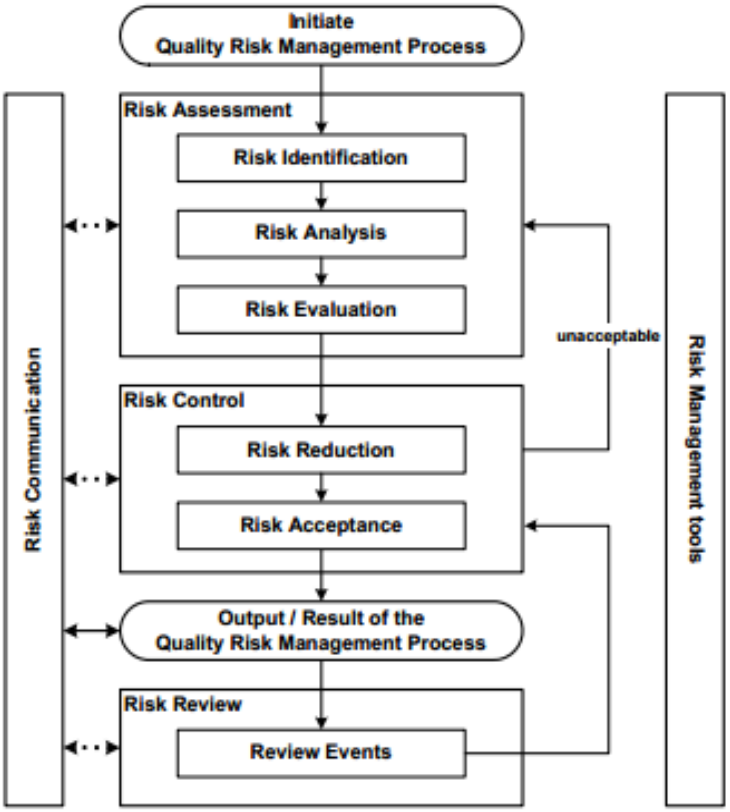

Figure 2: Quality risk management process

These are important caveats that should be remembered as risk assessment. It is a process that can easily be overused and lead to large amounts of unnecessary documentation. In Annex 1 to ICH Q9 the following tools are suggested for risk management in the pharmaceutical industry:

- Flow charts;
- Check sheets;
- Process mapping;
- Cause and effect diagrams;
- Failure mode effects analysis (FMEA);
- Failure mode effects and criticality analysis;
- Fault tree analysis;
- Hazard analysis and critical control points;
- Hazard operability analysis;
- Preliminary hazard analysis;

- Risk ranking and filtering;
- Various statistical tools:
- Acceptance control charts;
- DoE;
- Histograms;
- Pareto charts;
- Process capability analysis.

While acknowledging that the selection of quality risk management tools is dependent on specific facts and circumstances, Annex 2 to ICH Q9 suggested areas to which quality risk management tools could be applied by pharmaceutical companies, ranging across all operational areas from quality management to facilities maintenance and even final packaging and labelling. Of particular relevance to this review were the potential applications to the development phase of pharmaceuticals suggested by the ICH. Specifically, application of Quality Risk Management techniques was suggested to assess the critical attributes of raw materials, APIs, excipients and packaging materials, as well as to determine the critical process parameters for a manufacturing process. Other areas suggested for development were to assess the need for additional studies (e.g., bioequivalence and stability) in technology transfer and scale-up and to reduce the variability in quality attributes [7.3].

ICH Q10 Pharmaceutical Quality System – describes a comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization (ISO) quality concepts, includes applicable cGMP regulations, and complements ICH Q8 and ICH Q9 [10].

The Pharmaceutical Quality System had described four key elements:

- A process performance and product quality monitoring system;
- A corrective action and preventive action system;
- A change management system;
- Management review of process performance and product quality.

Importantly, the guideline emphasized that these elements should be applied in a manner 'proportionate and appropriate' for each of the stages of product life cycle. That is, the same level of rigor is not appropriate for products in the development stage as in the commercial or discontinuation phases of a product's life cycle. It was the regulators' hope that adoption of ICH Q10 should "facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities". Knowledge Management and Quality Risk Management were projected as 'enablers' of this innovation. While movement within a registered design space would not require regulatory approval, the change should still be evaluated and documented by the company's change management system [7,4].

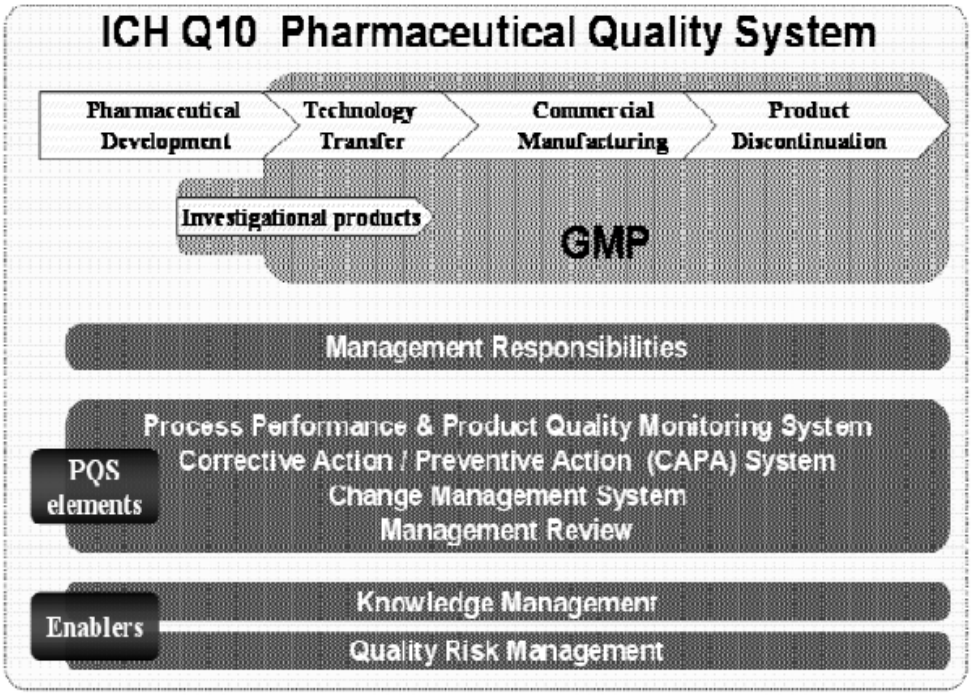

Figure 3: ICH Q10 Pharmaceutical Quality System Model

Elements of QbD

Four main elements of QbD are:

1. Risk assessment approaches which begin with mapping tools such as flow-down map, process map, Ishikawa diagram to evaluate their knowledge space and further risk management tools such as failure modes and effects analysis (FMEA).

2. PAT tools including in-process monitoring and multivariate systems.

3. Mathematical and statistical tools which can be used in the planning, designing and analysing the experiment: statistical design of experiments (DoE).

4. Continuous improvement tools which are implemented throughout process/product lifecycle to maintain the robust QbD construct [12].

Parallels between manufacturing process and analytical method development

A QbD approach to analytical method development has many parallels to QbD for product and process development. Table 1 gives the particulars. The overall approach emphasizes design to achieve the desired performance or quality attributes, process knowledge to understand the critical parameters that will have an impact on the quality of the final output, knowledge of variability in process inputs to establish appropriate controls, process monitoring to maintain control, and a continuous improvement with the foundation of the process knowledge that has been obtained [13].

Table 1: Parallels between Product development and analytical method development

Product/ process development	**Analytical method development**
Define desired product performance – identify critical quality attributes (CQAs)	Define capability requirements of method- what does the method need to do
Design product and process to meet CQAs	Choose technique and design method to meet capability requirements
Understand impact of material attributes and process parameters on product CQAs	Understand impact of method parameters on results obtained
Identify and control significant sources of variability in materials and process – risk assessment	Identify and control significant sources of variability in reagents, instrumentation, columns, etc. – risk assessment
Continually monitor and update process to ensure consistent quality	Continually monitor method performance and potential improvements to ensure validity of results

Method requirements

A key aspect of QbD is the definition of what the process or analytical method needs to do. At the highest level, methods should support patient needs and product requirements, especially since the methods do not add quality to the product itself. The methods are, however, critical in assessing the quality of the product and its performance relative to patient needs. Therefore, the methods are part of an overall well-designed control strategy that ensures the quality of the final product.

Method requirements can be thought of as the intended purpose of the method. This can be stated simply as "the method needs to determine moisture in an active pharmaceutical ingredient (API)" or "determine degradation products in a drug formulation", but further requirements need to be articulated to guide the design of the method. Generation of an "analytical target profile" (ATP) is suggested as a means to capture method requirements. These requirements often include the precision, range, accuracy, or sensitivity needed for the method. An example of this is "the method needs to determine related substance impurities in an API at levels between 0.05 and 0.20% with a standard deviation of 0.02%". Even more detail could be provided for requirements related to specific impurities [13].

Regulatory challenges and inspection

"In a QbD concept, the regulatory burden is less because there are wider ranges and limits based on product and process understanding. Changes within these ranges and limits do not require prior approval" [3,7].

Traditionally, inspections have been conducted using the FDA system-based approach and in accordance with CDER's Compliance Program "Inspection of Licensed Biological Therapeutic Drug Products". But now query arises that how the inspection will take place in the present scenario where QbD is mandated. During pre-license or preapproval inspections under a QbD concept, the FDA inspection team will assess the implementation and effectiveness of the process design as described in the application and whether knowledge and risk management have been transferred successfully from development to manufacturing. The inspection will evaluate the quality system and its effectiveness regarding consistent product quality, change in control

procedures, process improvements, deviation management, and knowledge and risk management during the product lifecycle. Inspection of facility and equipment qualification and maintenance as well as raw material screening and supplier management will be same as it was performed previously. But design, testing, and monitoring programmes that demonstrate robustness and consistency would be highlighted [2,8].

Basic considerations of QbD

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

Advantages of QbD can be summarized as,

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

Method design concept helps to avoid cost involved with post approval changes [12].

Elements of pharmaceutical development

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.

Different elements of pharmaceutical development include,

- Defining an objective
- Determination of critical quality attributes (CQA)
- Risk assessment
- Development of experimental design
- Designing and implementing control strategy
- Continuous improvement [2,8]

Define an objective

Quality target profile (QTP) forms the basis of QbD, which is in relation to the predefined objective criteria mentioned in the definition of QbD.

As per ICH guideline Q8 R2 the Quality Target Product Profile forms the basis for design and the development of the product. Considerations for the Quality Target Product Profile could include:

- Intended use in clinical setting, route of administration, dosage form, suitable delivery Systems.
- Dosage strength(s), container and closure system.
- Therapeutic moiety release or delivery and attributes affecting, Pharmacokinetic parameters (e.g., dissolution, aerodynamic performance).
- Drug product quality criteria like sterility, purity, stability and drug release as appropriate for dosage form the intended for marketing.

QbD requires a Target Product Profile; it may be called as Quality Target Product Profile (QTPP) which defines the expectations in the final product. In case of analytical method development it is called as analytical target profile (ATP), it is also called as Target Product Profile (TPP). The TPP can play a pivotal role in the entire drug discovery and development processes like optimization, planning and decision making, and designing of clinical research strategies. The Target Product Profile (TPP) can be used to design the clinical trials, safety and ADME studies, as well as to design the drug product. The TPP will help to identify critical

quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties [2,12].

Determination of critical quality attributes (CQA)

According to ICH Q8 R2 "A CQA 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 linked with the drug substance, excipients, intermediates (in-process materials) and drug product. For example CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability whereas for parenterals these are sterility and clarity. The CQAs can additionally include properties like particle size distribution, bulk density that affect drug product. Mostly CQAs are derived from the Quality Target Product Profile and/or prior knowledge is used to guide the product and process development and subsequently CQAs are assessed for risk management.

It is stated in ICH Q9 that in case of potential drug substance CQAs are used to guide process development. Inclusion and exclusion in list of potential CQAs can be done as knowledge drug substance and process understanding increases. In case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process. A quality attribute that must be controlled within predefined limits to ensure that the product meets its intended safety, efficacy, stability and performance. It means all the factors which affect final quality and safety should be controlled.

Dissolution test is crucial for a controlled release drug product and on the other hand dissolution test for an immediate release drug product which belongs to the high aqueous solubility and high permeability i.e. BCS class I drug will not prove as a critical attribute for quality control parameter. CQA differs depending on the type of process, dosage form, and type of method to be developed hence thorough knowledge of real time data to working scientists is important [2,12].

Risk assessment

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and its severity. Risk assessment helps to increase quality of method or process. Also it is determinant for effect of input variable on method or processes. From risk assessment one can recognize critical attributes that are going to affect final quality of product. A risk assessment is helpful for effective communication between FDA and industry, research/development and manufacturing and among multiple manufacturing sites within company. There may be risk and uncertainty in validation of bioanalytical method though the guidelines for validation are given by various regulatory bodies there may be a variation in interpretation of those guidelines and hence in experimental method designing which leads to unfit method development for intended purpose. Risk management for excipients to determine shelf life can be done by statistical parameters [3,7].

Principles of quality risk management are:

- Scientific knowledge based evaluation of the risk to quality which eventually links to the protection of the patient.
- Adequate effort should be taken; formality and documentation of the quality risk management process should be done with the level of risk involved.

Risk management is the joint responsibility of the quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical department.

Methods of risk assessment*:* Some methods of risk assessment are mentioned in ICH guideline Q9 as follows:

- Failure Mode Effects Analysis (FMEA); [14,15,16]
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);[17]
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);

- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

ICH guideline Q9 gives description of risk management and various terminologies associated with it, like Risk Acceptance, Risk Analysis, Risk Assessment, Risk Communication, Risk Control, Risk Evaluation, Risk Identification, and Risk Management. Quality management policies should mention procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk. Risk Reduction is actions taken to lessen the probability of occurrence of harm and the severity of that harm [3,12,18].

Development of experimental design

Experimental design is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Design space is proposed by the applicant and is subject to regulatory assessment and approval of ICH Q8 (R2). Pharmaceutical development scientists have begun making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing. Risk assessment can be a guide to understand linkage and effect of process parameters and material attributes on product, and ranges for variables within which consistent quality can be achieved. These parameters or attributes are selected for addition in the design space. Information regarding reason for inclusion of some variables in design space as well as exclusion of other variable has to be stated. Operation within the design space will result in a product meeting the defined quality. Independent design spaces for one or more unit operations can be applied; a single design space can be applied for multiple operations. For example impact of excipient variability on particle size distribution, blend segregation propensity can be included in experimental design. Different mathematical models are available for design of experiment like Placket–Burman, Box Behnken, Taguchi, Surface Design, Full and fractional factorial designs. Full factorial design was used to study the effect of formulation factors on pharmaceutical properties of tablet; in which independent variables were binder and disintegrant concentration, resistance to crushing while dependant variable was drug release. Such a multidisciplinary approach is beneficial as manufacturing process improvement can be done in

previously approved space; it decreases the number of variation after marketing. It is a risk based approach which is based on timely quality control rather than final testing of finished product [12,19].

Designing and implementing control strategy

Control strategy is required to ensure that material and process are within the expected lower and upper limits. Parameter and material are routinely controlled during production in order to assure reproducibility. The control space should be within the design space. Generally scale up is trial and error basis. During scale up processes parameters may differ but attributes which affect quality remains the same hence control strategy is required. QbD gives trace on reproducibility and robustness. Process capability index expresses reproducibility of process. [9]

$$Process\ capability\ index = \frac{upper\ limit\ of\ specification - lower\ limit\ of\ specification}{6\ standard\ deviation}$$

Control space should be within the design space, it is an upper and lower limit for raw material or a process within which parameter and material are regularly controlled which assures quality of product. Design space covers control space. If control space is smaller than design space it is considered as robust. Usually in-process quality control tests are performed to examine quality and trace out defects but QbD approach being proactive in the initial steps the potential attributes which could possibly give out of range result and affect the quality are identified. Deliberate variations in those attributes are studied in the design space. Control strategy involves but is not limited to – control on excipients, drug substance, packaging materials (inputs), specifications, operational control like drying downstream processing dissolution etc., real time testing or in process testing, finished product testing at regular intervals [12].

Continuous improvement throughout product life cycle

Product quality can be improved throughout the product lifecycle; companies have opportunities to opt inventive approaches to improve quality. Process performance can be monitored to make sure consistency in quality. Additional experience and knowledge is gained during routine manufacturing which contributes to method/process development. Periodic maintenance can be done within a company's own internal quality system; but design space should be unchanged.

The QbD approach avails the continuous improvement throughout products' life cycle this is a distinguishing point from the conventional method which is much frozen process [12].

CONCLUSION

The major objectives with regard to quality issues are addressed by the ICH guidelines. These are Q8 Pharmaceutical development, Q9 Pharmaceutical risk management and Q10 Pharmaceutical quality systems. Quality-by-design (QbD) is a new concept which has been added in the annex to guideline Q8. The QbD approach leads to enhanced understanding, well-defined system and regulatory flexibility. Well adoption of QbD tools is the key to achieve long-term benefits. Not to be disorientated among all aspects of QbD, appropriate risk assessment tools such as flow-down maps and Ishikawa diagrams can be considered in the beginning. It will be instructive to keep the processes in perspective. Tools of DoE and PAT should be determined based on the specific intentions and to make their outcome assessment capably, well-trained staff are necessary as well as for establishing a design space which requires mathematical and statistical knowledge. As shown with mentioned case studies, implementation area of QbD is extremely wide. QbD can provide extended knowledge about all phases in any drug's lifecycle. In product development studies, combination of several material attributes and unit operation parameters are evaluated. But, it is also possible to focus on only one unit operation such as fluidised bed granulation, roll compaction and tablet coating. With the contribution of different bodies of the pharmaceutical area, all of the case studies exemplify to encourage the implementation of QbD. As long as pharmaceuticals get more complex in the meaning of advanced manufacturing techniques and the new areas such as personalised medicine, the importance of a well-constructed quality system will gradually increase.

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