

Quality by design (QbD) for pharmaceutical area

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Abstract: Recent changes and limited resources for drug development and manufacturing have rendered the conventional pharmaceutical quality assurance approach insufficient and have given rise to new research in these areas. To address these research efforts, the FDA improved and modernized the rules governing pharmaceutical manufacturing and product quality in 2002, thereby realizing a paradigm change in the current Good Manufacturing Practices (cGMP). The Quality by Design (QbD) approach has entered the pharmaceutical industry within the last 10 years after the approval of the ICH Q8 in 2005. QbD is based on an understanding of the target product's quality profile (QTPP) and an assessment of its risks during the design and development of pharmaceutical dosage forms. By determining the critical quality attributes of the drug, including its active ingredient, its excipients, and the processes and design spaces used during the R&D phase, multi-way tracking during the life cycle of the drug can be achieved. This tracking can provide numerous advantages, including flexibility in licensing by decreasing the variation and type modifications in applications of the pharmaceutical product, which result from minimizing the possible issues arising after the release of the product. When all these data are observed, it is clear that the new QbD approach benefits the authorities, the drug manufacturers and the patient. Although QbD has certain challenges during its early stages, it is thought that QbD will benefit pharmaceutical manufacturers.

Keywords: Quality by design (QbD), target product quality profile, critical quality attributes, design space, risk assessment.

Introduction

An extreme increase in the number of requests, requirements, efforts and costs involved in the current drug licensing process has accompanied

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an ongoing increase in the complex practices and risks involved in the pharmaceutical industry. The complexities involved in drug manufacturing, which increase the risks of drug development, are very difficult to eliminate. Nonetheless, there is a need to correctly manage complexity and risk and regulate decision-making processes accordingly.

In the pharmaceutical industry, which tries to adapt to rapidly changing innovations, important developments have occurred in manufacturing information, quality management systems and risk management in recent years. Modern systems have also been developed to ensure product quality. These new tools allow drug manufacturers to detect, analyse, correct and prevent problems while continuously improving the drug manufacturing process. To encourage drug manufacturers to utilize these modern tools, to support the continuous improvement in manufacturing, and to constitute a regulatory environment, in 2002, the FDA introduced the Current Good Manufacturing Practices (cGMP) to the pharmaceutical industry, which were aimed at improving and modernizing the rules used to manage drug manufacturing and product quality.

1. A Scientific and Risk-Based Approach

cGMP represents a regulatory tool set with a wide scope (FDA, 2004). The application of risk-based cGMP brings innovations to the pharmaceutical industry, though this approach is not required as of yet. As a part of risk-based cGMP, the regulatory programmes that manage the manufacturing and control of the pharmaceutical and chemical industries aim to achieve the following goals (FDA, 2004):

- Encourage the pharmaceutical industry to develop new technologies,
- Support the industrial application of modern quality management techniques, including the practice of quality system approaches, in drug manufacturing and quality assurance,
- Encourage the application of risk-based approaches that focus the attention of both the industry and authorities on critical areas,
- Review the regulations and ensure that inspection policies and guidelines for complying with the rules are based on current pharmaceutical science, and

- Improve the consistency and coordination of regulatory programmes by integrating the advanced quality system approaches into the authority's regulatory policies regarding work processes, review and inspection activities.

The ICH forum consists of the licensing agencies in the USA, Japan and Europe as well as specialists from the pharmaceutical industry in order to harmonize the technical requirements of registering pharmaceutical products between the three regions. The ICH is also responsible for publishing current guidelines (Runas, 2008). In 2005, the ICH published the Q8 guideline (ICH Q8, 2009), which recommended the integration of the “quality by design (QbD)” concept into the pharmaceutical industry. Although QbD approach has been recently formalized in pharmaceutical industry, the concepts such as DoE, PAT have been applied for decades for better understanding, modeling and control of the processes.

It is known that the development of safe and efficient new treatments is a long, difficult and expensive process. With the use of the new approach (QbD), which ensures that the quality is provided by the manufacturing of a product instead of by product testing, the product quality is improved at decreased costs. QbD studies may also provide some income to the drug manufacturers even though QbD has faced certain challenges early in its development. Additionally, higher-quality drugs emphasize patient safety and ensure that the patient will obtain the drug in a shorter time.

As defined by ICH Q8, QbD is a systematic drug development approach that begins with pre-defined goals, implying that the understanding of the product and processes are based on sound science and quality risk management (ICH Q8, 2009).

As one of the system practices indicated for the future, QbD (Gaspar et al., 2012) also includes potentially valuable, patient-specific treatment practices along with conventional dosage forms, sustainable drug manufacturing practices, quantitative risk assessments in the pharmaceutical development processes that involve life cycle management and the downstream processing of biotechnological products (Aksu et al., 2012a).

2. QbD Practices

The quality of a pharmaceutical product depends on the safety of the molecule, its mechanism of effect, and an understanding of its biology. When QbD is used, the pharmaceutical quality is provided by the understanding and control of the formulation and manufacturing variables (Yu, 2008). When the product quality is “designed” instead of being “tested” (Arling et al., 2008), the manufacturing process is developed based on the required qualities of the molecule under development. In the QbD approach, existing information can be combined with data obtained from drug development studies in order to create a design space that provides sustainable development. Thus, changes made without the approval of authorities in the industry can be provided by changes in the control management.

The ICH Q8 guideline was published to regularize the QbD approach and to provide manufacturing flexibility to the molecule itself and to its manufacturing processes.

2.1. QbD Steps

The QbD development process (Figure 1) includes the following:

- QbD begins with a target product profile that defines the usage, safety and efficiency of the product.
- Formulators and process engineers then define the target product quality profile during the development of the product.
- Existing information regarding the active ingredients, excipients and processes is collected, and the risk assessment is used to prioritize the effect of information gaps and changes to the known facts about the product.
- Formulation and manufacturing processes are designed. The critical quality attributes of the finished product, which should be controlled to meet the target product quality profile, are determined.
- The critical process and formulation parameters that should be controlled to provide the critical quality attributes of the finished product are determined. Risk assessment is used to prioritize the

process and parameters that require experimental confirmation. To understand a design space or process, previously obtained information is combined with the experimental data.

- For the entire process, a control strategy that includes the entry material controls, the process controls and monitoring, the design spaces around single- or multi-unit operations, and/or finished product tests are developed.
- To provide consistent quality, the process is continuously monitored and updated.

The design of experiments (DoE), risk assessment and process analytic technology are tools that can be used in the QbD process when needed, but their application is not necessarily required.

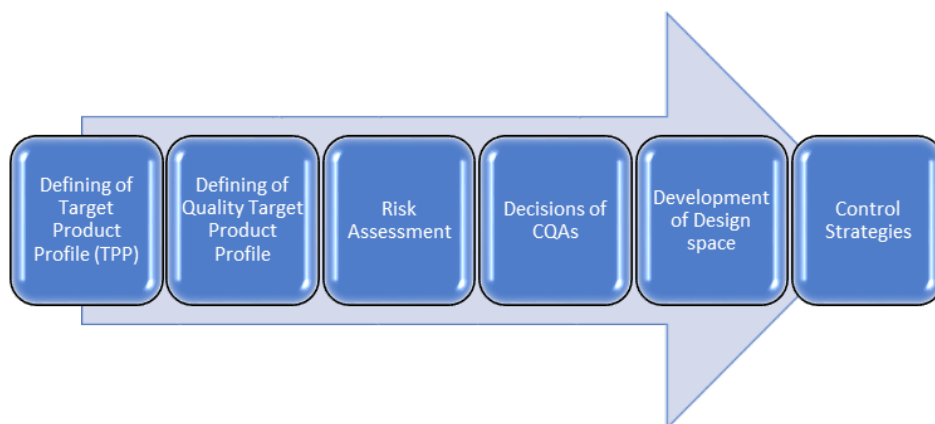


Figure 1. QbD development process

2.2. Design Targets

The first step of QbD is defining the design targets for the product.

2.2.1. Target Product Profile (TPP)

A Target Product Profile (TPP) explains the main purpose of a drug development programme and provides information regarding the development process. TPPs usually contain some specific concepts that are required to be on the drug label (FDA, 2007). ICH Q8 requires the “determination of critical attributes for the patent medicine quality

by considering the intended use and practice method”, and a product’s intended use and practice method is assessed using its TPP.

The TPP is a patient- and labelling-centred concept that can be thought as the “user interface” of patented medicine. Thus, the TPPs of a generic version and a reference product are expected to be the same. A generic product may use a different formulation or design in applying the TPP. The characteristics and performance tests of a patented medicine depend on special practices that may vary between the generic product and reference product. For a new drug, changes in the TPP may require new safety or efficiency data, though new data are not required for changes in the product characteristics or performance resulting from reformulation (FDA, 2007; Delasko et al., 2005).

2.2.2. Quality Target Product Profile (QTPP)

A target product quality profile, also called a quality target product profile (QTPP), consists of quantitative support for clinical safety and efficiency that can be used to design and optimize a formulation or manufacturing process (ICH Q8, 2009). The QTPP summarizes the attributes and characteristics of a product that dictate its quality. As a sub-branch of the TPP, which is published by the FDA, the QTPP is more focused on the chemical, manufacturing and control stages of development (Lionberger et al., 2008).

The QTPP defines the quantitative targets for the attributes of the drug (e.g., solubility, potency, impurity, stability) and includes specifications such as the dosage form, application way, packing, appearance and diagnosis. The QTPP includes the quantitative targets, release profiles and other product-specific performance requirements. For generic products, bioequivalence is included as a part of the QTPP. The QTPP is not a specification because specification includes tests for properties such as bioequivalence or stability, which are not carried out in the batch. The QTPP only includes the product performance related to the patient. For instance, if particle size is critical for the dissolution of solid oral product, then the QTPP should include the dissolution but not the particle size.

2.2.3. Critical Quality Attributes (CQA)

The base of the ideal dosage form is developed using the TPP. While designing the product and process, attributes such as the clinical performance and manufacturability are also important. Meeting these requirements in the TPP is a condition of QbD.

ISPE PQLI defines the critical quality attributes (CQAs) of a product in terms of its physical, chemical, biological or microbiological attributes/characteristics, which should be directly or indirectly controlled to ensure product quality.

The ICH defines CQA as follows: “CQA is the physical, chemical, biological or microbiological attribute or characteristic that should be directly or indirectly controlled to ensure that the product meets the desired safety, efficiency, stability and performance.” This definition indicates that the desired safety, efficiency, stability and performance are not part of CQA. Safety and efficiency are instead covered by the TPP (Singh et al., 2010).

2.3. Critical Process Parameters (CPP)

2.3.1. Process parameters

A parameter indicates the measurable or numerable characteristics of a system or process. Process parameters are attributes of the manufacturing system and are usually the characteristics of the equipment or processes related to manufacturing, such as the temperature and mixing rate. By contrast, attributes are considered the characteristics of materials (e.g., melting temperature, viscosity, sterility) (Mesut et al., 2015). However, it must be remembered that there are no absolute distinctions between attributes and parameters (Robert et al., 2008).

Because the process depends on the critical process parameters (CPP) and the critical material attributes (CMA), controlling the attributes of the output material may be a better control strategy than monitoring the operation parameters, especially in upscaling. For instance, a material attribute such as the humidity content should have the same target value in pilot and commercial processes. An operation parameter such as the flow rate is expected to change with process scale changes.

2.3.2. Classification of Process Parameters

Many material attributes and process parameters are necessary for the product quality, but not all parameters are critical.

The differentiation of attributes or parameters as critical and non-critical is important as a result of the development process and in deciding which attributes and parameters are to be included in the design space. An assessment and determination of the criticality of quality attributes or process parameters should be made based on their effects on the safety, efficiency or quality of the product. Here, the QbD elements are based on the risk assessment and are used to form a design space and develop a control strategy.

2.4. Design Space

At present, the FDA realizes the limiting attributes of existing drug development approaches and, along with ICH, supports the QbD concept. In accordance with this, the design space has a significant place in the pharmaceutical industry. A design space is defined as the “multi-dimensional combinations and interactions of process parameters where the quality and input substance variables (e.g., material attributes) are demonstrated to be secured. The design space is specific to a unit operation or a single manufacturing process, and it defines the operational process parameters (such as the humidity ratio) that are known to affect the product quality. The design space can also be thought of as the bond between CQAs and CPPs (Short et al., 2010).

The design space is a way to show the development of the understanding of a process, and the advantages of creating a design space are obvious. However, one of the challenges for the effective use of design space is the cost of its formation.

2.4.1. Development of a Design Space

The design space development process begins with an idea of the product to be obtained and continues throughout the life cycle of the product. The formation of a design space begins with the QTPP, which defines the performance characteristics required for the product. *** To

determine the experiments to be carried out for the first research studies, which aim at prioritizing the quality attributes and process parameters and are used along with previously existing information, a pre-risk evaluation is also recommended (Garcia et al., 2008).

In the formation of design space, model based information derived from demonstration and previous process information of the product are more effective than the effect of information coming from other products and processes.

The most important point in the development of a design space is proving or determining that unclassified parameters excluded from the DoE are truly non-critical process parameters and thus do not interact. Furthermore, it might be possible to define a normal operating range (NOR) for the non-critical parameters up to the proven acceptable range (PAR) based on trends and prior knowledge and the superposition of those parameters would be considered as part of the design space. Before beginning to create a design space, some effort should be made to decrease the number of classified process parameters. For this purpose, a screening DoE can be used to omit the meaningful interactions between process parameters. When there are no interactions between process parameters, single variable intervals are suitable for non-critical parameters, and they can be added to the design space without additional work.

A design space involves the proven acceptable intervals (PARs) for the CPPs and the acceptable values for the CQAs to which they are related. Because a design space has no effect on the target profile of the product, it is not necessary to include normal operation intervals (Lepore & Spavins, 2008).

Normal Operating Range (NOR): is a designated range, within the proven acceptable range (PAR), specified in the production instructions as the range within which a process parameter/s is/are controlled, while producing unit operation output material or finished product meeting critical quality attributes release criteria and Critical Quality Attributes.

Proven Acceptable Range (PAR): is a characteristic range of a process parameter for which operation within this range, while keeping other parameters constant will result in producing a material meeting relevant quality criteria [ICH Q8(R2)]. PAR is the upper and/or lower limits of a

range for process parameter values in which the parameter is expected to produce a process or unit operation output that meets the CQAs.

2.4.2. Design Space and Modelling

As previously mentioned, a design space defines the multi-variable functional relations between the CQA and the CPP and includes their relations to unit operations. These relations can be found by applying risk assessment, design of experiments (DoE) and modelling in addition to using the literature and previous information (Garcia et al., 2008).

Approaches for determining the design space include the following strategies (Schmitt, 2011):

- First principals approach – the modelling is performed by utilizing a combination of mechanical chemistry, physics, engineering and experimental data,
- Statistically designed experiments (DoE), and
- Upscaling correlation – a semi-experimental approach is used to understand the operational situations between different scales or equipment parts.

2.4.3. Risk Assessment Practices

The starting point for developing a design space is a risk assessment conducted to achieve a QTPP, which is accepted as an expression of the CQA acceptance criteria (Demir et al., 2015). Risk assessments are used to determine areas in which the risks involved in the process are acceptable. This assessment can also identify areas that require detailed efforts to decrease or control the risks. Finally, risk assessment is used to create more understanding in the case of an existing risk (ICH Q9, 2005).

2.4.4. Design of Experiments (DoE)

Parameters that should be included or excluded in multiple variable analysis and/or model development should be assessed and chosen by considering the significant differences between the process requirements for large and small molecules in addition to the differences between active

ingredients and finished product processes. When the process parameters are defined, the parameter number for multiple factorial analysis should be decreased. It may be time consuming and tedious to attempt to create a design space that includes all parameters that may affect the quality of the finished product. Thus, risk analysis tools can be used to indicate the parameters for which the risk of affecting a CQA in a finished product is decreased (ISPE, 2011).

2.4.5. Design Space and Scale-Related Problems

The design space is usually developed on the laboratory scale based on the small number of materials to be used, the ease of equipment use and the repeatability of experiments. Understanding the risks of upscaling the attributes and parameters in the design space indicates whether a study must be carried out to assess the suitability of the design space to a commercial scale.

As long as the aim is to ensure the desired product quality and process consistency, in case of scaling ups, it might be a better strategy to monitor and control the output material attributes rather than operating parameters. Due to the fact that operating parameters, such as liquid spraying rate or air flow rate in granulation operation would tend to change as process is being scaled up, it would be much reliable to control the output material moisture content (quality attribute) which should remain at the same target value for pilot and commercial process.

2.4.6. Licensing Flexibility Introduced by the Design Space

The application of a design space reflects the process information as it exists at that time, though additional information may also result in post-licensing changes. However, there is no need for an application/approval for the changes in the design space, a licensing situation that gives some space for the selected parameters but not granting any flexibility to other parameters occurs. This may change when the scale or equipment is changed. Stepping outside the design space may be viewed as a change requiring a post-licensing change (variation) process that is normally carried out (Lionberger et al., 2008; Garcia et al., 2008; Aksu et al., 2013a).

2.5. Control Strategy

Whether simple or complex, a control strategy should exist regardless of whether it is developed using a minimal approach or an advanced approach (QbD). In the most advanced products, finished product tests are relied on as a control strategy. In products developed using the QbD approach, in-line controls usually take the place of a control strategy (ISPE, 2011).

A control strategy is defined as a set of planned controls derived from current product and process information that secure the process performance and product quality (ICH Q10, 2008).

2.6. QbD and Control Strategy

Even though the control strategy is not a new concept, in the new approach emerging within QbD, a control strategy is closely related to both criticality and design. In the QbD approach, the control strategy requires more understanding of the product and process. QbD also provides more information than the minimal approach, thereby increasing the control strategy options for areas requiring more time and specialty.

Pharmaceutical quality is ensured by understanding and controlling the formulation and manufacturing variables that affect the quality of the finished product. Finished product tests only confirm the product quality.

2.6.1. Control Strategy During Pharmaceutical Development

Developing an effective control strategy should be risk-based to ensure that the product quality requirements are met. Developing the control strategy begins with the QTPP. The first studies are aimed at characterizing the active ingredient and the important physical, chemical, biological and microbiological attributes of the formulation. During this stage, the process development is also defined. For example, if the active ingredient has low water solubility, it is important that the immediate release tablet form provides sufficient dissolution of the drug. Toxicity studies performed during the first stages provide a starting assessment of the impurity profile of the active ingredient. Understanding the formation and removal of impurity, in which stages the control strategy elements will take place, developing the acceptance criteria and methods to be included

in specifications will provide an important point of view (ISPE, 2011).

Though a control strategy should be developed using these steps, it can also be formed using the quality risk management principles defined in ICH Q9.

2.6.2 Applying Control Strategies to Manufacturing

During manufacturing, the understanding of a process that includes the durability of control strategy continues to increase. The application of product and process review systems during the commercial manufacturing process within the pharmaceutical quality system should provide opportunities for updating, modifying or continually improving the control strategy.

If necessary, a pharmaceutical quality system should be updated to support the use of the QbD approach in the control strategy. When the product information, documents, operation procedures and systems must be changed, a pharmaceutical quality system should provide the appropriate technical and administrative audits required for obtaining the necessary assessments and approvals (ISPE, 2011).

2.6.3 Benefits of forming a QbD-based Control Strategy

The costs of quality risk assessments, analytical techniques and control systems should be balanced with the investment income required during manufacturing.

In methods that include PAT applications in QbD, the non-initiative methods usually decrease the exposure of operators to chemicals and/or potentially dangerous products; sustainability is supported by the use of environmentally friendly practices. Because the tests necessary to release the batch are reduced through the use of online and inline techniques, the costs required for the removal and recycling of waste solvents are reduced and the analysis times are shortened. With the application of a control strategy in which the advanced approach is used, the continuous improvement of the process is ensured and the possibility of defective batches is reduced (ISPE, 2011).

PAT or real time process monitoring along with conformance to QbD specifications based on parametric modelled Design Space's output acceptance quality criteria also take place in Real Time Release Testing. Just to point out that, a real time monitoring differs from PAT by encompassing only designing and analysing a manufacturing process, but not controlling the process as in PAT.

Real Time Release Testing: is the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of assessed material attributes and process controls [ICH Q8(R2)] (PQRI, 2015).

3. Solutions and Benefits Brought by QbD

QbD practices provide an overall win-win-win policy. From the manufacturer's perspective, QbD can provide a better understanding about the product or process can be used to develop more efficient processes and can reduce licensing requirements. It is important to regulators that licensing flexibility can be provided without compromising quality. Moreover, because the focus is always on the patient, this approach can also increase the quality of the product. The PAT initiative is a very important quality step in the pharmaceutical industry. Applying PAT to new manufacturing processes or existing manufacturing processes will provide benefits in terms of competitive differentiator and in relieving the pressure of the cost which is the main challenge for the industry.

In a summary, there are many studies conducted for different dosage forms which emphasize the advantages of QbD vs. traditional approach (Mesut et al., 2013; Aksu et al., 2012b, c; Aksu et al., 2013b, c; Aksu et al., 2014; Güngör et al., 2013).

On the other hand, analytical methods take significant role when using QbD approach during pharmaceutical process development and production. Furthermore, analytical testing take role in risk assessment, process monitoring and control and continuous quality assessment throughout the product life cycle (Dasare, 2013). Similarly to the implementations mentioned above, the same principles of QbD approach can be applied to develop analytical methods. The difference mainly reflects in used terminology, such as Analytical Target Profile (ATP) instead of Quality

Target Product Profile (QTPP), Critical Method Attributes (CMA) instead of Critical Quality Attributes (CQA) and etc. Studies, like (Bracke et al., 2015) and (Hubert et al., 2015) can be referred for such implementations of AQbD approach.

The benefits of QbD for the pharmaceutical industry can be summarized under the following topics (Aksu, 2013d).

Increasing manufacturing efficiency: QbD increases the efficiency of manufacturing due to the factors listed below:

- Linking manufacturing with the clinic during design,
- Improving the design of less problematic products during manufacturing,
- Improving the understanding of how active ingredients and excipients affect manufacturing,
- Decreasing the variability included in a project,
- Solving technical problems,
- Increasing productivity by preventing losses,
- Making continuous improvements in products and manufacturing processes,
- Decreasing overall manufacturing costs, quality costs and waste,
- Decreasing the number and complexity of analysis texts, and
- Bringing real-time releases into effect.

Recommending licensing flexibility: Licensing flexibility can be introduced by applying the QbD principle to an existing product. By understanding the processes better, the approval time of the authority is shortened and the number of audits is decreased. This flexibility is also valid for studies of biotechnological products because it recommends a design space, which is explained in ICH Q8 (R1) and consists of the following:

- Decreasing the manufacturing supports required for post-licensing changes,
- Applying new technologies without the licensing consent,

- Facing fewer challenges during the audit and obtaining faster approval, and
- Reaching a scientific agreement between the authorities and the industry.

Operation strategy: QbD provides some benefits to operational strategies, including the following:

- Using the “latest technologies” in manufacturing,
- Guaranteeing and increasing the quality level from unit to unit,
- Reducing the number of documents,
- Reducing the risk,
- Collecting and integrating real-time data,
- Managing information, and
- Achieving a better overall work model.

Result

With the QbD approach, the product quality is not tested at the end of the manufacturing process. Instead, quality is designed during the product design and is integrated into the final product. Quality assurance is a superior method to quality control, and in QbD, quality is assured rather than controlled.

As continuous process improvements have become possible, QbD has emerged as an approach in which the manufacturing process performance for process validation is continuously monitored, assessed and adjusted.

With this new approach, decisions can be taken and executed with scientific and risk-based information.

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